DISSERTATION ON

A STUDY OF PREVALENCE OF AUTONOMIC DYSFUNCTION IN TYPE- 2 DIABETES MELLITUS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations
for the award of the degree of

M.D. IN GENERAL MEDICINE

BRANCH – I

THANJAVUR MEDICAL COLLEGE,

THANJAVUR - 613 004

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

APRIL -2016

CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY OF PREVALENCE OF AUTONOMIC DYSFUNCTION IN TYPE – 2 DIABETES MELLITUS''** is the bonafide original work of **Dr. IVAN A JONES** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu Dr.M.G.R. Medical University to be held in APRIL - 2016. The period of the study was from January – 2015 to August -2015.

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DECLARATION

I, **Dr.IVAN A JONES,** solemnly declare that dissertation titled **" A STUDY OF PREVALENCE OF AUTONOMIC DYSFUNCTION IN TYPE-2 DIABETES MELLITUS"** is a bonafide work done by me at Thanjavur Medical College and Hospital during January 2015 to August 2015 under guidance and supervision of my unit chief **Prof.Dr.K.NAGARAJAN, M.D.,** Professor and head of the Department of Medicine.

This dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine.**

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INTRODUCTION

Diabetes Mellitus, a disease characterized by hyperglycaemia caused by absolute or relative deficiency of insulin. The pancreatic hyperglycaemia associates with various functional and morphological alterations which affect almost all systems of the body.

Before insulin was discovered, diabetic patients died of acute metabolic complications like ketoacidosis, lactic acidosis, or hyperosmolar nonketotic coma. With the invention of insulin and oral hypoglycaemic agents many of the late complications of diabetes have been documented as the patient's life span increases. These include the involvement of the eye, kidney, heart, blood vessels, cerebral, peripheral and autonomic nervous system. These late complications lead to considerable morbidity and mortality.

Although diabetic retinopathy, nephropathy and neuropathy are well known, autonomic neuropathy is the most neglected aspect of diabetic late complications due to difficulties in diagnosis related symptoms are unclear, no symptoms in earlier stages, and lack of specific treatment.

The earliest reference to diabetic neuropathy was in the first century by Cadaeus. He postulated that paresthesia in arms is a sign of neuropathy and Rayfus proposed it as a possible feature of diabetic autonomic neuropathy. Invention of simple noninvasive techniques by Ewing DJ and the newer investigative techniques of cardiovascular heart rate monitoring given by Wheeler and Watkins have shown patients who had established cardiac autonomic neuropathy in diabetes. This might lead to sudden myocardial infarction, altered response to physiological and pathological stress and sudden cardiorespiratory arrest leading to deaths in diabetic patients. The incidence and

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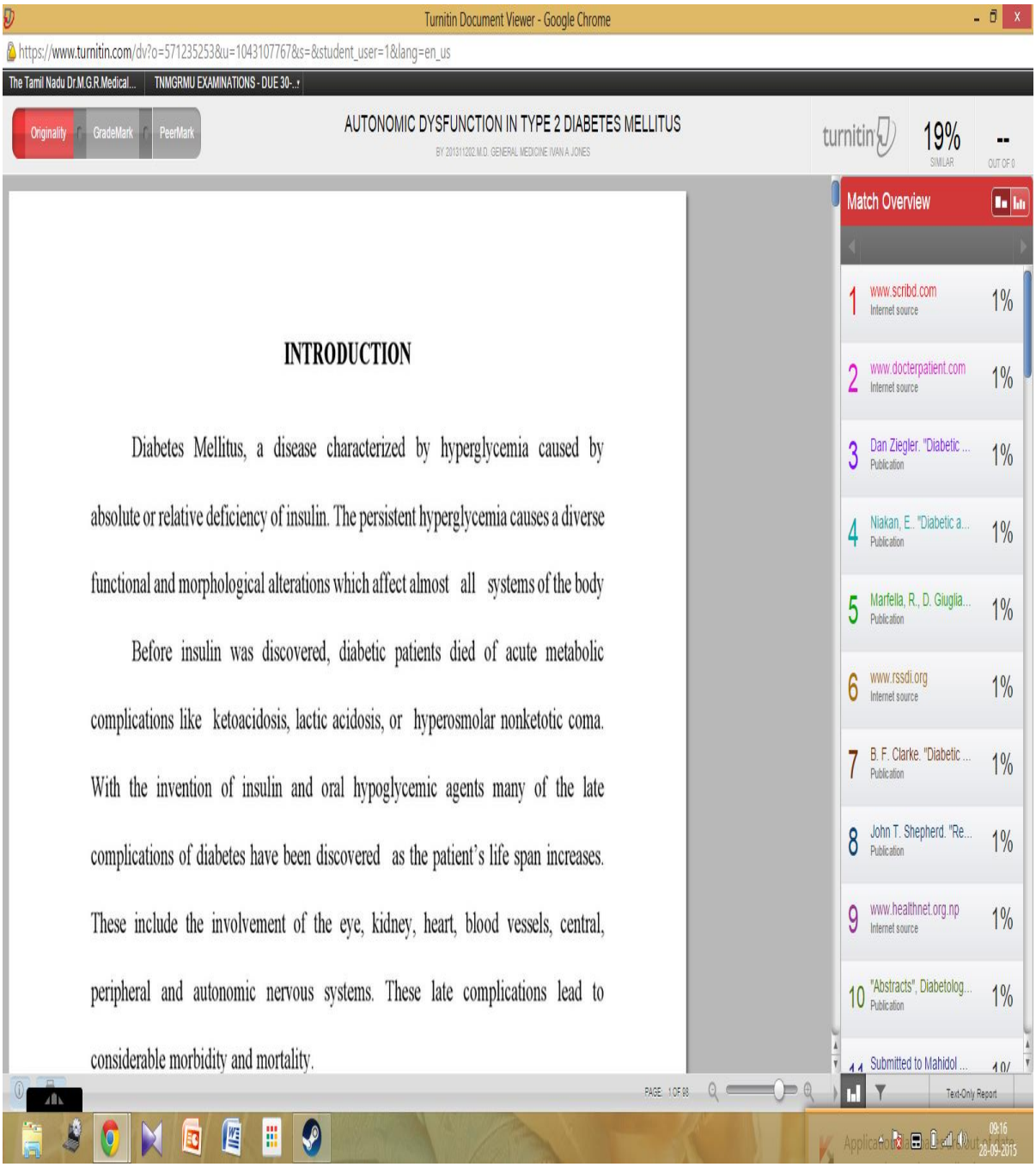
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ABBREVIATIONS

Sn-Serial Number

Ipn-In patient number

Doa-Date of admission

Drn-Duration of diabetes

Reg-Regularity of treatment

DOC-Degree of control

Ht-Height

Wt-Weight

Bmi-Body mass index

Ph-Postural hypotension

Gf-Gastric fullness

Nd-Nocturnal diarrhoea

Cn-Constipation

Us-Urinary symptoms

Im-Impotence

Tn-Tingling and Numbness

Kn-Knee jerk

An-Ankle jerk

Ec-Eye changes

Rh-Resting heart rate

Deep Breathing test:

Dbi, Dbe - Inspiration, Expiration

Ei_ra- EI ratio

(R-R Int.msec)

Ei__r- EI test result

LYING TO STANDING TEST:

Ls_15,Ls_30-15th,30th beat

Ls_ra-30th/15th beat ratio

(R-R int.in msec)

Lr-Lying to standing result

SQUATTING TEST:

Sql,Sq2,Sq3- R-R intervals phases I,II,III

Sqtv- Vagal ratio

Sqtv- vagal test result

SqTs- Sympathetic ratio

S - Sympathetic test result

CONTENTS

A STUDY OF PREVALENCE OF AUTONOMIC DYSFUNCTION IN TYPE- 2 DIABETES MELLITUS

AUTHOR: Prof. Dr.K.Nagarajan, **Dr.IVAN A JONES**

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BACKGROUND: Autonomic neuropathy is the most neglected aspect of diabetes due to difficulties in diagnosis, which requires invasive investigations in earlier days, and lack of specific treatment. Most earlier studies have been done on autonomic dysfunction in Type I Diabetes mellitus and there are only a few studies on Type II Diabetes mellitus patients. With this in mind, this study has been conducted on the prevalence of autonomic dysfunction in Type II Diabetes mellitus patients and the association of various factors with this disease in the diabetic population in and around Thanjavur.

AIMS & OBJECTIVES: To study the prevalance of autonomic neuropathy in previously diagnosed and newly detected patients with Type 2 diabetes mellitus in Thanjavur.

METHODS: 40 type 2 Diabetes mellitus patients and 10 control subjetcs who were admitted in Thanjavur medical college were enrolled in the study. Those who complied with the inclusion and exclusion criteria were subjected to detailed history taking and clinical examination and necessary investigations was done and analysis was performed with appropriate statistical methods.

RESULTS: 90% of patients studied had prevalence of diabetic autonomic neuropathy. A battery of tests is more accurate in assessing the degree of involvement of the autonomic system rather than a single test. Among the tests performed, the heart rate response to deep breathing and to postural change from lying to standing were found to be the most sensitive in detecting prevalence of autonomic neuropathy

CONCLUSION: This study revealed a high prevalence of autonomic neuropathy in Type2 Diabetes mellitus patients. This was also evident even in asymptomatic patients. The squatting test can be used as an early marker of dysautonomia. The degree of metabolic control was the factor which had the strongest association with severity of autonomic impairment. Thus, this study underscores the value of tight metabolic control in the management of Type2 Diabetes mellitus.

KEY WORDS: Valsalva manoeuvre, heart rate changes, squatting test.

INTRODUCTION

Diabetes Mellitus, a disease characterized by hyperglycemia caused by absolute or relative deficiency of insulin. The persistent hyperglycemia causes a diverse functional and morphological alterations which affect almost all systems of the body

Before insulin was discovered, diabetic patients died of acute metabolic complications like ketoacidosis, lactic acidosis, or hyperosmolar nonketotic coma. With the invention of insulin and oral hypoglycemic agents many of the late complications of diabetes have been discovered as the patient's life span increases. These include the involvement of the eye, kidney, heart, blood vessels, central, peripheral and autonomic nervous systems. These late complications lead to considerable morbidity and mortality.

Although diabetic retinopathy, nephropathy and neuropathy are well known, autonomic neuropathy is the most neglected aspect of diabetic late complications due to difficulties in diagnosis, which requires invasive investigations in earlier days, and lack of specific treatment.

The earliest reference to diabetic neuropathy was in the last century by Eichorst. He postulated that persistent tachycardia is due to vagal neuropathy and Rundles proposed it as a possible feature of diabetic autonomic neuropathy..Invention of simple noninvasive techniques by Ewing DJ. and the newer investigative technique of continuous heart rate monitoring given by Wheeler and Watkins has shown gross abnormalities of cardiac autonomic innervation in diabetes. This might lead to painless myocardial infarction, altered response to physiological and pathological stress and sudden cardiorespiratory arrest leading to death in diabetic patients. The

incidence and extent of autonomic nervous disease in the population tends to be grossly underestimated.

This could be due to the relatively subtle manifestations, the gradual onset and progression, and that several of these complications occur in those patients who have other co-morbid diseases. The tests for autonomic neuropathy are neither well-known nor widely practised, despite the fact that simple bedside clinical tests of cardiovascular function correlate well with other system involvement by diabetic autonomic neuropathy.

Most earlier studies have been done on autonomic dysfunction in Type I Diabetes mellitus and there are only a few studies on Type II Diabetes mellitus patients. Type II DM in Indians have many interesting features which includes high prevalance , strong correlation with genetic factors , with less common obesity and earlier onset of diabetes .

With this in mind, this study has been conducted on the prevalence of autonomic dysfunction in Type II Diabetes mellitus patients and the association of various factors with this disease in the diabetic population in and around Thanjavur.

AIMS OF THE STUDY

1. To study the prevalance of autonomic neuropathy in previously diagnosed and newly detected patients with Type 2 diabetes mellitus in Thanjavur .
2. To study the prevalance of symptomatic and asymptomatic autonomic impairment in Type II Diabetes Mellitus.
3. To analyse the involvement of parasympathetic and sympathetic system in Type 2 Diabetes mellitus patients with autonomic nervous system damage.
4. To analyse the correlation between cardiovascular responses and age, sex, body mass index, duration of the disease and degree of metabolic control.
5. To find the correlation between autonomic impairment and proteinuria.
6. To assess the correlation between hypercholesterolemia and autonomic neuropathy.
7. To study the influence of type and regularity of treatment on the severity of autonomic neuropathy in Type 2 Diabetes mellitus patients.
8. To establish the efficacy of the squatting test as an early marker of autonomic impairment.

REVIEW OF LITERATURE

HISTORY OF DIABETES MELLITUS

Diabetes was described about 2000 years back. Aretaeus of Cappadocia (About 150 AD) called the disease and referring to it as Polyuria, gave the name "DIABETES"- coming from the Greek words meaning ” To run through ” (Dia - Through, Bainein - To go) because he observed that the disease comprised of " a liquefaction of flesh and bones into urine "

In 1674,Thomas Willis discovered (by tasting it) the fact that the urine of a diabetic person was sweet, " As if infused with honey (MELLITUS)" .This was a rediscovery since an ancient Hindu Document by Susrutha in India about 4000 BC has described a condition "Madu Meha " the diabatic syndrome consisting of a "Honeyed Urine ". Willis could not name the chemical nature of the sweet substance.

In 1776, Mathew Dobson showed that the sweet substance in diabetic urine is ‘’sugar’’. This led to a’’ rational dietary approach’’ introduced by Rollo about 29 years later. Morton (1686) mentioned the hereditary character of diabetes .In 1859 Claude Bernard showed the increased glucose content of diabetic blood. In 1869 Langerhans, a medical student described the islets in the pancreas which was then named after him. In 1874 Kussmaul described the airhunger of the diabetic patients in coma.

In 1889 Von Mering and Minkovski demonstrated that dogs could get diabetis by pancreatectomy. In 12th January 1922 Fredrick Banting and Charles best prepared active extract of pancreas in the lab which was capable of lowering blood glucose levels. The first patient who received this pancreatic active extract was Leonad

Thomson, a boy aged 14 years. It took 30 more years for the development of procedures for purifying and modifying insulin.

In 1936 Hagedorn introduced the first long acting insulin.

In 1955 Banger and co-worker delineated chemical structure of insulin.

In 1967 Steiner and Oyer discovered proinsulin molecule.

In 1977 Insulin gene cloned (Ulrich, Rutter, Goodman, and Co—workers).

In 1982 With the invention of recombinant technology insulin became the first hormone to be produced by genetic engineering.

In modern day medicine most of the complications of diabetes were widely investigated. Urinary bladder dysfunction due to diabetic neuropathy was first described in 1864 by Marchal Decalvi.[7] In 1885 Pary reported a case of a diabetic patient with absence of sweating. Buzzard (1890) and Auche (1890) two other observers noted vasomotor and trophic disturbances due to peripheral autonomic dysfunction in diabetic patients.

Haemoglobin A1c was initially separated from other forms of haemoglobin by Huisman and Meyering in 1958 using a chromatographic column. It was described as a glycoprotein by Bookchin and Gallop in 1968. Its increase in diabetes was first described in 1969 by Samuel Rahbar and coworkers.The reactions during its formation were characterized by Bunn and his co-workers in 1975. The use of hemoglobin A1c for monitoring the degree of control of glucose metabolism in diabetic patients was proposed in 1976 by Anthony Cerami, Ronald Koenig and coworkers.

ANATOMY AND PHYSIOLOGY OF AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system is present throughout the central and peripheral nervous system and it consists of two parts, the sympathetic system and parasympathetic system. There are afferent and efferent nerve fibers in both systems. The peripheral motor portion of the autonomic nervous system consists of preganglionic and postganglionic nerves.

SYMPATHETIC SYSTEM

The sympathetic outflow of central nervous system extends from the first thoracic segment to second lumbar segment (sometimes third lumbar segment).

PREGANGLIONIC FIBERS

The cell bodies of pre ganglionic nerves are located at intermediolateral grey coloumn of spinal cord. The myelinated axons of these neurons leave the spinal cord through ventral roots of the first thoracic to third lumbar spinal nerves.

They pass through white rami communicantes to the paravertebral sympathetic ganglion chain, where most of these axons end on the cell bodies of the post ganglionic neurons which it enters.

Some of these fibers pass upwards or downwards in the chain and synapse in one of the other ganglion of the chain. Other fibers pass through one of the spinal nerves and terminate in the prevertebral ganglia.

SYMPATHETIC CHAIN

This lies close to the vertebral column and consist of a series of sympathetic ganglia mostly having a segmental arrangement. There are 3 cervical, 11 thoracic, 4 lumbar and 4 sacral ganglia- all paired together with 1 unpaired coccygeal ganglion.

POST GANGLIONIC FIBRES

These fibers mainly arise from ganglion cells either in the sympathetic ganglia or in the prevertebral ganglia and pass through the corresponding spinal nerves through grey rami supplying various organs. These fibers are unmyelinated C fibers.

AFFERENT PATHWAY

The afferent myelinated nerve fibers travel from the viscera through the sympathetic ganglion without synapsing and enters the spinal nerves through the white rami and reach their cell bodies in the dorsal root ganglia. The central process enter the spinal cord and forms the afferent component of local reflex arc.

PARASYMPATHETIC SYSTEM

The parasympathetic outflow consists of cranial and sacral outflow.

EFFERENT OUTFLOW

The cell bodies of preganglionic parasympathetic nerve fibres are located in the brain stem and sacral segments of the spinal cord. The nerve cells which are located in the brain stem form parts of nucleus of origin of the following cranial nerves.

- The oculomotor (Edinger westphal nucleus).
- The facial (Superior salivatory nucleus).
- The glossopharyngeal (Inferior salivatory nucleus).
- The vagus (Dorsal nucleus of vagus)

The axons of these nerve cells emerge from the brain stem travel in the cranial nerves. The sacral connector nerve centers are located in grey matter of the 2nd, 3rd and 4th sacral segments of the cord. The myelinated axons leave the spinal cord in the

anterior nerve roots of the corresponding spinal nerves and form the pelvic splancnic nerves.

The preganglionic fibres synapse in the peripheral ganglia, usually situated close to the viscera which they innervate. These ganglia include the ciliary, pterigopalatine, submandibular and otic ganglia. In certain conditions the ganglion cells are diffusely arranged in nerve plexus such as cardiac plexus, pulmonary plexus and in the myenteric plexus of the gastrointestinal tract. The post ganglionic fibres are short and innvervate the viscera.

THE AFFERENT FIBRES

The afferent fibres mainly travel from the viscera to their cell bodies which are located either in the sensory ganglia of the cranial nerves or in the posterior nerve root ganglia of the sacrospinal nerves. The principal afferent fibres of the parasympathetic system reach the central nervous system through the vagus nerve.

HIGHER CONTROL OF THE AUTONOMIC NERVOUS SYSTEM

The higher nervous centre that control the lower autonomic centers in the brain stem and spinal cord is situated in the hypothalamus. Stimulation of the anterior hypothalamus influences parasympathetic responses and stimulation of posterior part evokes the sympathetic responses.

The lower brainstem centers such as the vasodilator, cardioaccelerator, cardiodecelerator centers are situated in the reticular formation of the cerebellum. It is believed that the various levels of control are exerted as a result of the interconnection of different regions by the ascending and descending pathways.

CENTRAL NERVOUS SYSTEM THAT INTEGRATE CARDIOVASCULAR REFLEXES

The afferent traffic from the arterial, cardiopulmonary mechanoreceptors and chemoreceptors that travel in the glossopharyngeal and vagal nerves has relays in the petrosal and nodose ganglia respectively and terminate in the nucleus tractus solitarious of the medulla. The cardiac vagal nonmyelinated afferents seem to project to the same part of the nucleus tractus solitarious as the myelinated fibres. This nucleus also has input from many other sites, including receptors in the skeletal muscles, the trigeminal and vestibular nerves,the hypothalamus and the locus cereleus. This array of afferent connections makes the nucleus tractus solitarious an important integratory center for reflex control of cardiovascular system.

Of all the higher centres in the brain, the hypothalamus has an important role in arterial blood pressure control. It has multiple connections with the cardiovascular neurons in the brain stem and also has connections that reach preganglionic neurons directly.

RECEPTORS IN THE SKELETAL MUSCLE[9]

A strong static (isometric) contraction of the skeletal muscles or a rapid, powerful, rhythmic contraction leads to a pronounced increase in arterial pressure and heart rate. This increase in perfusion pressure helps to combat the mechanical compression of the vessels by the contracting muscle.

When static contraction is performed with one forearm, there is an immediate increase in heart rate and arterial pressure which is followed by a continued gradual increase in pressure.

The rapid increase in the heart rate at the onset of exercise and return to control when contraction stops is similar to a " central command" signal from the motor cortex to the brain stem cardiovascular centers. In addition to this, there may be a rapidly acting excitatory input from group III mechanoreceptors in the contracting muscle. Studies in human subjects suggest that the rapid changes in the heart rate are caused primarily by reduction in the vagal tone. The changes in the arterial pressure at the onset of contraction are secondary to a combination of increase in the cardiac output and systemic vascular resistance.

Claude Bernard in 1863 showed that the sympathetic system plays the important role in the continuous adjustment of overall performance of cardiovascular system. If the heart is denervated but the sympathetic nerves to the systemic vessels are intact, the myocardium becomes supersensitive to the circulatory norepinephrine that enters the blood from peripheral nerve endings resulting in increase in heart rate and contractility.

Figure 1 - THE AUTONOMIC NERVOUS SYSTEM

Blue : Parasympathetic Red : Sympathetic

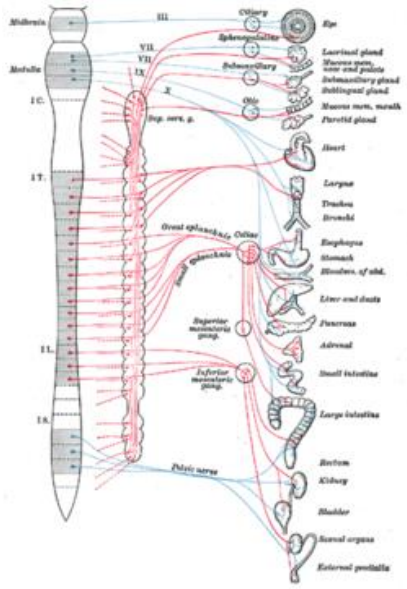
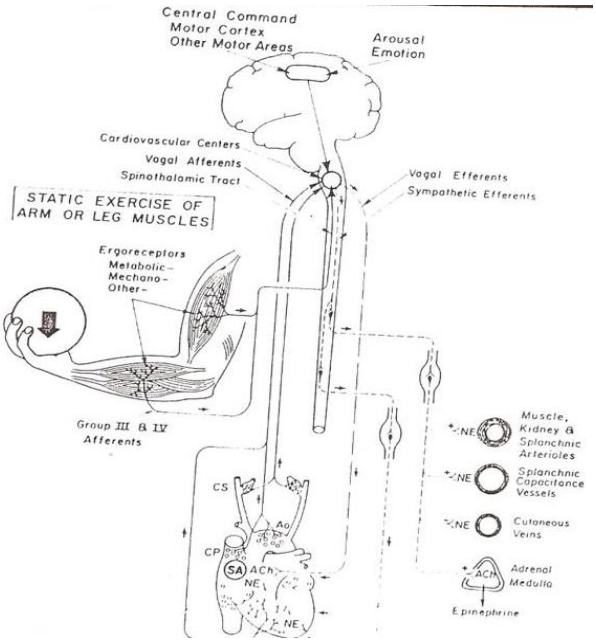


Figure 2 Factors involved in the cardiovascular response to the static exercise.

CS – Carotid Sinus NE – Norepinephrine SA – Sinoatrial node Ao – Aortic arch Ach – Acetylcholine CP – Cardiopulmonary receptors



THE ARTERIAL BAROREFLEX

The baroreceptors of the carotid sinus and aortic arch acts in such a way as to inhibit the vasomotor center tonically. When the pressure in the carotid sinus is decreased, the resultant decrease in afferent nerve activity causes an increase in arterial pressure. This alteration is caused from augmented sympathetic activity to the heart and blood vessels and diminished vagal activity to the heart. An increase in heart rate and cardiac contractility follows together with constriction of resistance vessels in muscle, kidney, splanchnic bed, skin and of the splanchnic capacitance vessels. The contraction of resistance vessels increases the total systemic vascular resistance and resulting in an increased after load on the heart. The constriction of capacitance vessels helps in maintaining the filling pressure of the heart and hence the Stroke volume, thus it maintains the cardiac output. When the pressure within the carotid sinus is increased, the reverse is true.

AUTONOMIC EFFECTS ON VARIOUS ORGANS OF THE BODY

Circulatory system

Heart

Organ	Sympathetic	Parasympathetic
cardiac output	β1, (β2): enhanced	M2: depressed
SA node: heart rate (chronotropic)	β1, (β2) [3]: enhanced	M2: depressed
Atrial cardiac muscle: contractility (inotropic)	β1, (β2)[3]: enhanced	M2: depressed
Ventricular cardiac muscle	β1, (β2): increase in contractility (inotropic) increase in cardiac muscle automaticity [3]	---
at AV node	β1: enhances conduction enhances cardiac muscle automaticity [3]	M2: depresses conduction Atrioventricular block [3]

BLOOD VESSELS

Organ	Sympathetic	Parasympathetic
vascular smooth muscle	α1: contracts; β2: relaxes	M3: relaxes [3]
renal artery	α1[4]: constricts	---
larger coronary arteries	α1 and α2[5]: constricts [3]	---
smaller coronary arteries	β2:dilates [6]	---
arteries to viscera	α: constricts	---
arteries to skin	α: constricts	---
arteries to brain	α1[7]: constricts [3]	---
arteries to erectile tissue	α1[8]: constricts	M3: dilates
arteries to salivary glands	α: constricts	M3: dilates
hepatic artery	β2: dilates	---
arteries to skeletal muscle	β2: dilates	---
Veins	α1 and α2 [9] : constricts β2: dilates	---

OTHER

Organ	Sympathetic	Parasympathetic
platelets	α2: aggregates	---
mast cells - histamine	β2: inhibits	---

RESPIRATORY SYSTEM

Organ	Sympathetic	Parasympathetic
smooth muscles of bronchioles	β2: relaxes (major contribution) α1: contracts (minor contribution)	M3: contracts

NERVOUS SYSTEM

Organ	Sympathetic	Parasympathetic
Pupil dilator muscle	α1: contraction (mydriasis)	M3: relaxation (miosis)
Ciliary muscle	β2: relaxation	M3: contraction

Digestive system

Organ	Sympathetic	Parasympathetic
salivary glands:	β: stimulation of viscous, amylase secretions α1: stimulation of potassium cation	M3: stimulates watery secretions
lacrimal glands	β2: secretion of protein[10]	M3: increases
kidney (renin)	β1: [11] secretion	---
parietal cells	---	M1: Gastric acid secretion
liver	α1, β2: glycogenolysis, gluconeogenesis	---
adipose cells	β1[11], β3: stimulates lipolysis	---
GI tract (smooth muscle) motility	α1, α2[12], β2: decreases	M3, (M1) [3]: increases
sphincters of GI tract	α1 [11], α2 [3], β2: contracts	M3: relaxes
glands of GI tract	no effect [3]	M3: secretes

ENDOCRINE SYSTEM

Organ	Sympathetic	Parasympathetic
pancreas (islets)	α2: decreases secretion from beta cells, increases secretion from alpha cells	M3[13] increased secretion from alpha and beta cells
adrenal medulla	N (nicotinic ACh receptor): secretes epinephrine and norepinephrine	---

URINARY SYSTEM

Organ	Sympathetic	Parasympathetic
Detrusor urinary muscle of bladder wall	β2: relaxation	M3: [11] contraction
urethral sphincter (internal)	α1: contraction	Relaxation
sphincter	α1: contraction; β2 relaxation	M3:[11] relaxation

REPRODUCTIVE SYSTEM

Organ	Sympathetic	Parasympathetic
uterus	α1: contracts (pregnant[3]) β2: relaxes (non-pregnant[3])	---
genitalia	α1: contracts (ejaculation)	M3: erection

INTEGUMENTARY SYSTEM

Organ	Sympathetic	Parasympathetic
sweat gland secretions	M: stimulates (major contribution); α1: stimulates (minor contribution)	---
erector pili	α1: stimulates	---

PHYSIOLOGY[10]

Stimulation of sympathetic system leads to widening of palpeberal fissure, pupillary dilatation, tachycardia and peripheral vasoconstriction, which inturn causes rise in blood pressure, inhibit peristalsis in the alimentary canal , contracts the sphincters of alimentary canal and bladder and produces piloerection and sweating. Sympathetic excitation causes secretion of adrenaline from the adrenal medulla leading to rise in blood pressure.

Stimulation of parasympathetic system causes pupillary constriction, bradycardia, vasodilatation, bronchoconstriction, secretion of tears and saliva, increased intestinal peristalsis and contraction of bladder and plays a principal part in sexual activity.

Sympathetic nerves are adrenergic and most of the parasympathetic nerves are cholinergic.

PATHOGENESIS OF DIABETIC NEUROPATHY

Many of the experimental and clinical studies, which have been recently reviewed in detail, have provided new thoughts into the pathobiochemical and pathophysiological mechanisms which form an important part in the pathogenesis of diabetic neuropathy. Five major pathogenetic concepts currently implicated in the pathogenesis are: —

1. Enhanced flux through the polyol pathway with increased aldose reductase activity leading to accumulation of sorbitol, depletion of myoinositol and reduction in Na^+ - K^+ - ATPase activity- Both these biochemical alterations and experimental diabetic neuropathy are prevented by administration of aldose reductase inhibitors.[11]

2. Reduction in the nerve blood flow and endoneural microvascular abnormalities with consecutive ischemia or hypoxia and enhanced generation of oxygen free radicals. These abnormalities associated with experimental diabetic neuropathy are prevented by different classes of vasodilators, gamma-linoleic acid and antioxidant treatment.

3. Formation of non-enzymatic advanced glycosylation end-products (AGEs) in nerve and vessel-wall proteins.[13] Aminoguanidine, a competitive inhibitor of AGE products normalizes the fall in nerve blood flow and abnormalities associated with experimental diabetic neuropathy.[14]

4. Deprivation of nerve growth factor (NGF) and other neurotropic factors and defects in axonal transport. The decrease in nerve growth factor is experimentally reversed by establishing normoglycemia.[15]

5. Immunological processes. A speculative mechanism is based on the theory that insulin antibodies may cross-react with nerve growth factor, which is required for the growth and survival of sympathetic nerves. Since nerve growth factor and insulin share similar antigenic determinants, the action of insulin antibodies may cause damage to sympathetic nerves. [16]

Other immunological phenomena consists of increased levels of circulating immune complexes and complement breakdown products (CBD) suggesting complement activation. In addition, the levels of activated T lymphocytes may be higher, proposing that cell mediated immunity may also play a part.[17] Also identified are antibodies to nervous tissues such as sympathetic ganglia, adrenal medulla and vagus nerve.

Recently Barzilay et al have reported an increased predilection in subjects with HLA BR3/4 to develop autonomic dysfunction.[18]

Autoantibodies to glutamic acid decarboxylase (GAD) have been seen in small groups of type I diabetic patients with peripheral and/or autonomic neuropathy. However recent studies were unable to endorse this first report in patients with cardiac autonomic neuropathy.[19]

NEUROPATHOLOGICAL CHANGES IN DIABETIC AUTONOMIC NEUROPATHY

Appenzeller et al described distended ganglion cells also known as "Giant sympathetic neurons" and shortened internodal distances in white rami communicantes of the paravertebral sympathetic chain.[20]

Olsson Y et al described vacuolations of neurons and club-shaped enlargement of neural cell processes in autonomic sympathetic ganglia.[21]

Low PA et al and Olsson Y et al stated demyelination of preganglonic sympathetic fibres. Kristensson et al described similar changes in the Vagus nerve. [12,21]

Subsequently Duchen LW et al established the distended or vacuolated neurons and enlarged cell processes in superior cervical and coeliac sympathetic ganglia. They also described severe loss of myelinated axons in sympathetic trunk and vagus nerve in patients with Autonomic Neuropathy along with inflammatory cellular infiltration by lymphocytes and macrophages circulated in relation to autonomic nerve bundles and ganglia.[22]

Tamura et al reported a decreased mean myelinated fibre density in the carotid sinus nerve, a purely afferent branch of the glossopharyngeal nerve, providing a possible neuropathological basis for the baroreceptor dysfunction in diabetic patients.[23]

Also stated are nerve fibre thickening, fibre fragmentation and decrease in the number of autonomic nerve fibres of the heart muscle in diabetic patients who underwent painless myocardial infarction. This led to the theory that a lesion of the

afferent nerves that conduct pain could be responsible for the lack of pain in these patients.[24]

Morphological studies of the vasa nervorum in the small nerve fibres from diabetic patients gave evidence for autonomic neuropathy of the vasa nervorum that could result in defective circulatory autoregulation.

DISTRIBUTION OF AUTONOMIC NEUROPATHY

By means of Electrophysiological testing, autonomic dysfunction can be seen in many diabetics without any other symptoms. Cardiovascular reflex abnormalities can be seen shortly after diabetes has been diagnosed and in asymptomatic diabetics of longer duration.[12]

Cardiovascular involvement is more common than any other system involvement. Postural hypotension is a late feature. Diabetics along with symptoms of autonomic neuropathy usually have other complications, mainly peripheral neuropathy. Both afferent and/or efferent pathways may be affected.

Cardiac parasympathetic function can be damaged without detectable sympathetic damage, but not the contrary.[12] Cardiac parasympathetic fibres are involved more expansively and earlier than sympathetic nerves.

CLINICAL PRESENTATIONS

Although destruction to the autonomic nerves involves almost all parts of the body, the effect is most apparent clinically in the cardiovascular system. The autonomic symptoms are often imprecise and present insidiously, the bulk of diabetics with autonomic neuropathy may go undetected for a considerable time. Over a period of years the symptoms may evolve into the elaborate picture of diabetic autonomic

neuropathy which has been well detected since then accounted by Rundles (1945), with a combination of other conditions like postural hypotension, nocturnal diarrhoea, gastric problems, bladder symptoms, abnormal sweating, impotence and a failure to detect hypoglycemia.[2]

ASSESSMENT OF CARDIOVASCULAR EFFECTS IN DIABETIC AUTONOMIC NEUROPATHY

Clinical Manifestation

Three cardiovascular abnormalities that have usually been linked with autonomic neuropathy are resting tachycardia, postural hypotension and "painless" or "silent" myocardial infarction.[8]

1.Heart rate changes:

A resting tachycardia and a fixed heart rate are typical findings in diabetic patients with cardiovascular autonomic neuropathy.

A large number of studies have described resting heart rates of 90-100 beats/min and sometimes heart rate increments upto 130 beats/min have been seen in combination with diabetic cardiovascular autonomic neuropathy. An average increase of 10 beats/min was detected in diabetics when likened with controls. The patients with parasympathetic damage have highest resting heart rates , while those with evidence for combined vagal and sympathetic involvement showed lower rates.

A fixed heart rate, defined as unresponsiveness to moderate exercise, stress or sleep specifies almost complete cardiac denervation.[26]

In one of the series only 1 of 64 patients showed a comparatively fixed heart rate during 24 hours of ambulatory monitoring, but even in this case a small heart rate variation is noted.

This outcome is similar to the situation encountered during pharmacological blockade and in the transplanted heart in which marginal heart rate variation can still be found perhaps due to intracardiac modulatory mechanisms of parasympathetic and sympathetic reinnervation.[28]

2. Postural Hypotension

Postural hypotension, documented as the clinical hallmark of autonomic neuropathy in diabetic patients, was described decades earlier.· Clinically it is characterized by dizziness, blackouts or visual impairment and even syncope following change from the lying to the standing posture. Randomly, postural hypotension is defined as fall in systolic blood pressure greater than 20 mm hg.

Venous pooling in the legs leading to decrease in cardiac output and arterial pressure is the normal result of standing up. Reflex vasoconstriction and cardiac acceleration therefore results to restore the blood pressure. In diabetics a failure to raise systemic vascular resistance by vasoconstriction, particularly in the splanchnic area and in the subcutaneous tissues is mainly responsible for postural hypotension. This may be due to damaged sympathetic innervation of resistance vessels along with loss of reflex vasoconstriction.[30]

3.**Silent Myocardial Infarction**

Occurrence of both symptomatic and asymptomatic coronary artery disease is raised in diabetic patients. Cardiac autonomic neuropathy is accountable for an altered perception of myocardial ischemia, painless myocardial ischemia and silent infarction.

ASSESSMENT OF CARDIOVASCULAR REFLEX ABNORMALITIES IN DIABETICS

Before the year of 1970 most tests to observe the autonomic nervous system were compound, invasive and often disagreeable. Presently there are many simple and non invasive tests to assess autonomic neuropathy.

These tests are as follows:-

1. Beat to beat variation
2. Heart rate response to standing from lying position
3. Valsalva manoeuvre
4. Blood pressure response to standing
5. Blood pressure response to sustained hand grip.
6. Heart rate response to atropine
7. Squatting test

These tests are based on cardiovascular reflex and are applied to assess parasympathetic and sympathetic function.

1. DEEP BREATHING TEST

The beat to beat variation depends on parasympathetic innervation. lt is most clear with slow heart rates or during deep breathing. It is decreased by faster heart rates, in older subjects, in the presence of cardiac failure and after development of intracranial lesion.

During deep breathing the subject lying quietly breathes deeply at 6 breaths per minute, a rate that causes a maximum variation in heart rate and the changes are

recorded with an ECG machine. The difference between the maximum and minimum heart rate gives the difference. 15 beats per minute variation or more is normal and 10 beats per minute or less is abnormal. Two modification of this technique have been defined. The first measures the "E I ratio", the mean of the longest RR interval during expiration to the mean of the shortest R-R interval during inspiration. The second modification is to measure maximum and minimum heart rates from an ECG during a period of deep breathing and record the difference.

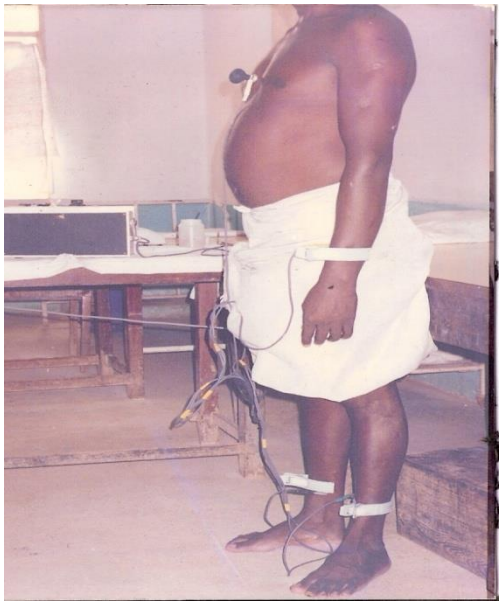
2. HEART RATE RESPONSE TO STANDING

Change of posture from lying to standing produces an assimilated cardiovascular response, including changes in heart rate; there is a distinctive and rapid increase in heart rate maximal at about the 15th beat after standing with subsequent relative bradycardia maximal at about 30th beat. Diabetics with autonomic neuropathy shows only a gradual increase or no increase in the heart rate. Pharmocologic studies specify that this response is arbitrated by the vagus nerve. This reflex response can be simply computed with continuous ECG recording and measurement of R-R intervals at beats 15th and 30th after standing to give the 30th/15th ratio.

In normal subjects value is greater than 1.03, whereas in diabetics with autonomic neuropathy values are 1.00 or less. The test is objective, simple, reproducible and not dependent on age or the resting heart rate.

DEEP BREATHING TEST

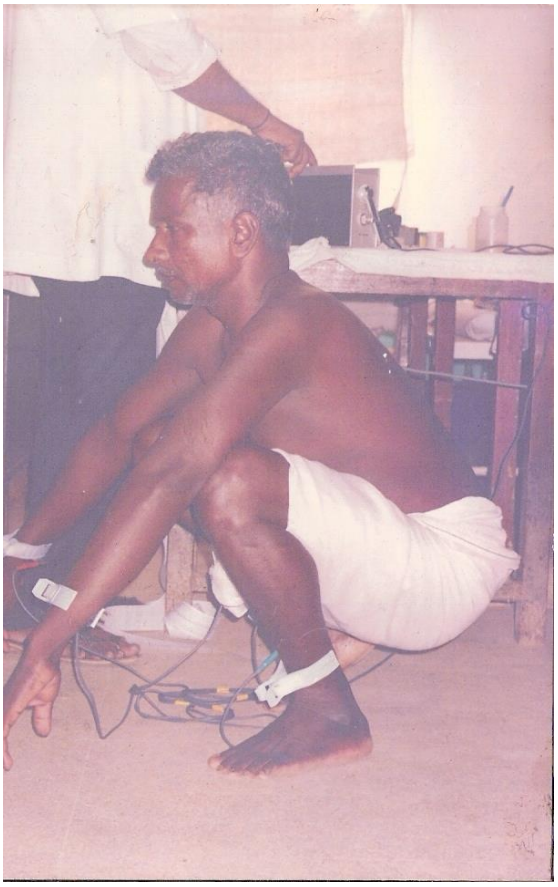
LYING TO STANDING TEST



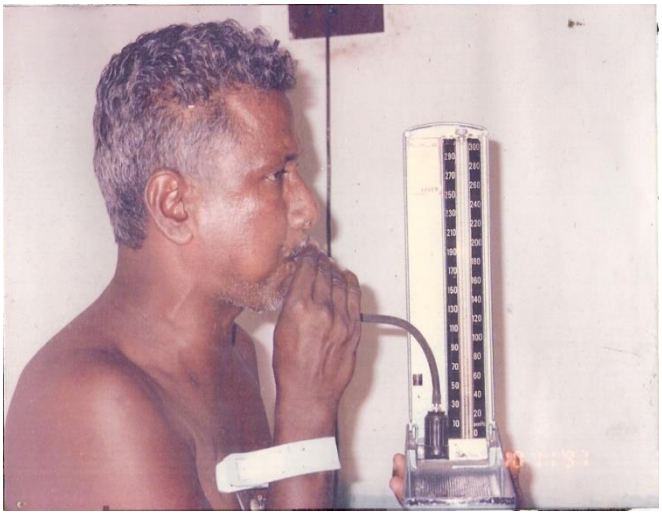
IV ATROPINE TEST

HAND GRIP TEST

SQUATTING TEST



VALSALVA MANOEUVRE



3.VALSALVA MANOEUVRE

The heart rate rises and blood pressure falls during the strain period of valsalva manouvre . After release blood pressure promptly rises over shooting its resting value and there is slowing of the heart rate . In the event of autonomic damage blood pressure falls during the strain period and there will be slow return to normal after release without any overshoot rise in blood pressure and there will be no change in heart rate . Previously , intraarterial pressure changes have been standard assessing . The heart rate changes give a reliable guide to the associated hemodynamic events .

The technique involves the subjects blowing into a mouth piece connected to a manometer held at 40mm of HG pressure for 15 sec, while a continuous ECG is recorded. The Valsalva ratio is calculated from the ratio of longest R-R interval after the manoeuvre (within 20 beats after the manoeuvre) to the shortest R-R interval during the manoeuvre.[27]

The Valsalva ratio of 1.21 or greater is normal, 1.11 to 1.20 is borderline and 1.10 or less is abnormal.[34]

4. BLOOD PRESSURE RESPONSE TO STANDING

A patient on standing, immediate pooling of blood occurs in the legs with fall in blood pressure .This is rapidly adjusted by reflex vasoconstriction and tachycardia. A decrease in Systolic blood pressure of 20mm of Hg upon standing is defined as abnormal, fall in 11 to 20 mm of Hg is border line and 10 mm of Hg or less is normal. The normal ranges and reproductivity of the most commonly used autonomic reflex test has been assessed by several investigators.

5.BLOOD PRESSURE RESPONSE TO SUSTAINED HAND GRIP

Sustained muscular exercise typically causes a heart rate dependent rise in Cardiac output, an increase in systemic blood pressure

and no change in peripheral vascular resistance.

A simple test based on this reflex uses a hand grip dynamometer standardised at 30% of the maximum voluntary contraction with measurement of the blood pressure during hand grip.[37] Patients with autonomic neuropathy have an abnormally small diastolic blood pressure rise. A rise in diastolic pressre of 10mm of Hg or lesser is abnormal and 11 to 15 of Hg is border line and 16 mm of Hg or greater is normal.

6. HEART RATE RESPONSE WITH DRUGS

Drugs that decrease parasympathetic tone like atropine causes a rise in the heart rate. Beta blockers decrease the heart rate by reducing the sympathetic tone. In diabetics with autonomic neuropathy the effects of these drugs are blunted or abolished.

7.THE SQUATTING TEST

The effect of squatting in terminating the attack of faintness in cyanotic patients was first noted by William Hunt in 1784 . This effect was then explained by Sharpey Schafer who noted increase in systemic arterial pressure followed by bradycardia due to reflex vagus effect, in normal individuals assuming squatting position from standing . It was also noted when a person stands from a squatting posture there is a decrease in arterial pressure followed by increase in heart rate as a result of sympathetic reflex .

Thus a single test which involves change in position between squatting and standing can assess both sympathetic and parasympathetic activity based on resultant cardiac rate .

The SqTv vagal ratio is the ratio between the base line R-R interval (mean of 10 beats) during phase-I and longest R-R interval in the first 15 sec of phase – II(squatting). The SqTs sympathetic ratio is the ratio between base line R-R interval

and the shortest R-R interval in the first 10 to 20 second of phase – III(standing from squatting).

It has been studied that patients with diabetic autonomic neuropathy have values are less than 99% lower confidence interval for SqTs ratios and greater than 99% higher confidence interval for SqTv ratios.

In patients with mild or no autonomic involvement , the SqTv ratio was significantly better than for deep breathing or lying to standing whereas the inverse true in case of severe autonomic involvement.

OTHER CLINICAL MANIFESTATION

1. GASTRO INTESTINAL SYSTEM

Diabetic autonomic neuropathy can involve the whole of the gut and several reviews have been published regarding this postulation.

OESOPHAGUS :

Symptoms relating to oesophagus are unusual. Infrequently dysphagia and heart burn occur in diabetic autonomic neuropathy. Motility disturbances are well recognized despite the lack of symptoms.

Decreased pharyngeal and oesophageal peristalsis after swallowing and reduced tone of the oesophageal sphincter are noted using manometric techinques by Taub et al, , 1979.

STOMACH :

Kassander (1938) established that 1/5th of the asymptomatic patients had gastric distension demonstrated by radiology and he commended the term "GASTROPARESIS DIABETICORUM" to describe this picture. The symptoms

have been well documented by Taub et al[40] and are often ill-defined with anorexia and epigastric fullness after eating. These occur due to vagus nerve dysfunction.

GALL BLADDER:

While enlarged and poorly contracting gall bladder were observed in diabetic autonomic neuropathy by Clark et al 1979,[8] in a study using ultrasonography. Marumo et al (1982) observed impaired gall bladder contraction following stimulation.

SMALL INTESTINE :

The characteristic episodic nocturnal diarrhoea of autonomic neuropathy has been well documented. The pathophysiology of the condition is not clearly understood. Proximal small intestinal motility disturbances involving both sympathetic and parasympathetic innervation have been well described in diabetics with gastroparesis. Excessive bacterial growth occurs following intestinal stasis is seen in some patients.

Bile salt malabsorption has been recommended as a likely mechanism[42]. Alpha-2 adrenergic receptors on small intestinal enterocytes have been found to be denervated in experimental diabetics recently. It might be a possible mechanism for diabetic diarrhea as they are thought to be responsible for fluid and electrolyte absorption .

LARGE INTESTINE :

Constipation is relatively common symptom of autonomic neuropathy. It is probably a result of colonic atony due to vagus nerve dysfunction.

II.BLADDER DISTURBANCES

Bladder dysfuntion is one of the common manifestations of autonomic neuropathy with an incidence of 26% to 87%. (Firimodt 1980).[56] There is gradual onset of symptoms and patients are usually asymptomatic for a long time.. Symptoms include decreased frequency of micturition, blunted sensation of bladder fullness, straining, hesitation, weakness of stream.[44] Later overflow incontinence maybe seen. These symptoms are ascribed to the damage of sensitive afferent sympathetic and parasympathetic fibres supplying vesical wall along with the S2-S4 segmental centres in the spinal cord.

III.SEXUAL DISTURBANCES

IMPOTENCE :

The incidence of impotence in diabetes is almost 50%. The preservation of libido is the striking feature of diabetic impotence . In sexual function in males, erection is under controlled by parasympathetic nerves and ejaculation is controlled by sympathetic system.[45]

The parasympathetic nerves (Erigentes) plays an improtant role in the enlargement of Corpora Cavernosa and Corpora Spongiosa. The impotence in male is due to lesion in the parasympthetic nerves of the Corpora Cavernosa and Corpora Spongisoa . .lt may also be due to reduced penile blood flow due to Atherosclerosis.

RETROGRADE EJACULATION :

Retrograde ejaculation is attributed to sympathetic nerve dysfunction. In diabetic patients with sympathetic neuropathy, orgasm occurs without accompanying ejaculation, as the semen is forced into the bladder due to relaxed internal vesical sphincter. The diagnosis is confirmed by the presence of semen in the post-coital urine.

IV-SWEATING DISTURBANCES

Diminished or absent sweating of the feet and in more severe cases the whole leg and lower trunk is well documented as a feature of diabetic autonomic neuropathy.[8] This may be due to lesion of sympathetic fibres.

Gustatory sweating noted by Agenaes 1962, later detailed by Watkins (1973)[47] is a further abnormal sweating pattern seen in diabetic autonomic neuropathy. Profuse sweating usually starts on the forehead and then spreads to the face, scalp and neck with in a minute of eating tasty foods notably cheese. The mechanism is uncertain but it has been suggested that aberrant nerve regeneration occurs within the territory supplied by the superior cervical ganglion.[47]

V.HYPOGLYCEMIC UNAWARENESS

Some diabetics with autonomic neuropathy lose their usual adrenergic early warning symptoms of hypoglycemia, so called "Hypoglycemia unawareness" and may suddenly become unconscious as they develop hypoglycemia.This maybe due to inadequate counter regulatory hormonal responses mediated by both vagal and sympathetic nerves. There may be steeper decrease of blood glucose than usual contributing to more rapid loss of consciousness.

VI.PUPILLARY DISORDERS

Rundles in 1945[2] noted abnormal pupillary responses caused by autonomic damage in diabetics. Both sympathetic dysfunction of dilator pupillae and parasympathetic dysfunction of sphincter pupillae are involved. The main clinical abnormalities are a reduction in pupil diameter at rest and loss of spontaneous

oscillation ("HIPPUS") of the Pupil.[49] A common and early sign of diabetic autonomic neuropathy is failure to dilate quickly in the dark.

VII PERIPHERAL NEUROPATHY

The clinical manifestation of somatic neuropathy includes symmetrical polyneuropathy, asymmetrical motor diabetic neuropathy and mononeuropathy. According to Ewing DJ et al 1981 autonomic neuropathy rarely occurs independent of peripheral neuropathy. Other workers have also reported 100% incidence of peripheral neuropathy.

The most common symptoms are pain and paraesthesia in the feet and hands. The signs include loss of tendon reflexes in the lower limbs and "Glove and Stocking" impairment of all modalities of sensation.

The diagnosis of peripheral neuropathy is confirmed by measuring nerve conduction velocities in both motor and sensory fibres.

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
A. Immune mediated
B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
A. Genetic defects of β-cell function
B. Genetic defects in insulin action
C. Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis

7. Others
D. Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others
E. Drug- or chemical-induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. α-Interferon
11. Others

F. Uncommon forms of immune-mediated diabetes
G. Other genetic syndromes sometimes associated with diabetes
1. Down's syndrome
2. Klinefelter's syndrome
3. Turner's syndrome
4. Wolfram's syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others
IV. Gestational diabetes mellitus (GDM)

Patients with any form of diabetes may require insulin treatment at some stage of the disease. Use of insulin does not, of itself, classify the patient.

Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.

MATERIALS AND METHODS

This study comprises of 40 Type 2 diabetes mellitus patients (26 males and 14 females). 10 healthy volunteers (relatives of patients), 6 males and 4 females were studied for age and sex matched control.

All the patients were admitted in Thanjavur medical college hospital and studied as in patients.

The age range of study population varies from 40 years to 79 years- The population studied was divided into four groups according to age groups as follows:-

1. 40 to 50 years
2. 51 to 60 years
3. 61 to 70 years
4. 71 to 80 years

The duration of diabetes of the population studied ranges from 0 to 20 years. Patients are divided into five groups as follows:—

1. <1 year
2. 1 to 5 years
3. 6 to 10 years
4. 11 to 15 years
5. >15 years

ACCORDING TO FASTING BLOOD GLUCOSE VALUES THE SUBJECTS STUDIED WERE DIVIDED INTO THREE GROUPS AS FOLLOWS:-

Measurement	Good control	fair control	poor control
HbA1c %	<6.5	6.5-7.5	>7.5
fasting plasma glucose (mg/dl)	90-104	105-130	>130

I. good control

II. Fair control

III. Poor control

The duration of diabetes and the type of treatment of the known diabetic subjects were taken from the patients file. The diabetic status of the known diabetic patients as well as the newly detected diabetic patients was assessed by estimation of fasting blood sugar and post prandial blood sugar after 75 gm of oral glucose load.

The newly detected patients were diagnosed as Type2 Diabetes mellitus according t o the criteria laid down by Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183-97.

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS AND IMPAIRED GLUCOSE HOMEOSTASIS

DIABETES MELLITUS - positive findings from any two of the following tests on different days:

Symptoms of diabetes mellitus* plus casual† plasma glucose concentration >=200 mg per dL (11.1 mmol per L)

or

FPG >=126 mg per dL (7.0 mmol per L)

or

2hrPPG >=200 mg per dL (11.1 mmol per L) after a 75-g glucose load

IMPAIRED GLUCOSE HOMEOSTASIS

Impaired fasting glucose: FPG from 110 to <126 (6.1 to 7.0 mmol per L)

Impaired glucose tolerance: 2hrPPG from 140 to <200 (7.75 to <11.1 mmol per L)

NORMAL

FPG <110 mg per dL (6.1 mmol per L)

2hrPPG <140 mg per dL (7.75 mmol per L)

Adapted from Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183-97.

†--Casual is defined as any time of day without regard to time since last meal.

*--Symptoms include polyuria, polydipsia or unexplained weight loss.

FPG=fasting plasma glucose; 2hrPPG=two-hour postprandial glucose.

INCLUSION AND EXCLUSION CRITERIA

1. Newly detected as well as known diabetic patients were included in the study.
2. Patients with coronary artery disease, cardiac arrythmia , valvular heart disease and cardiac failure were excluded from the study.
3. Patients with previous history of myocardial infarction were excluded.
4. Known hypertensive patients and patients with airway disease were excluded.
5. Patients with central and peripheral nervous system disease except those associated with Type 2 DM were excluded from the study.
6. Patients who are on beta blockers, ACE inhibitors, calcium channel blockers, digitalis and other drugs likely to affect the autonomic function were excluded.
7. Patients with any other chronic illness were also excluded.

By means of structured questionnaire patients were asked questions aimed at assessing the presence of the following symptoms of autonomic neuropathy.

1. Dizziness/vertigo/postural instability on standing.
2. Regional hypohidrosis/hyperhidrosis.
3. Dysphagia/vomiting/post-prandial gastric fullness/ nocturnal diarrohea
4. Diminished bladder sensation/decreased frequency of micturition hesitation and weakness of urinary stream / urinary incontinence.
5. Impotence in males.
6. Tingling and numbness of extremities.

Symptoms were scored as present or absent. If there was any doubt regarding any symptom it was scored as absent. Symptomatic autonomic neuropathy was considered to be present if one or more symptoms are present.

ASSESMENT OF METABOLIC CONTROL

Recent trends favour the use of glycosylated hemoglobin as the most sensitive indicator of metabolic control. In an analysis of 4000 patients Chandalia et al reported that glycosylated hemoglobin provides a different interpretation as compared to blood glucose in about half of the diabetes. He suggested that such a difference is more marked in Type1 diabetes mellitus patients who tend to have greater fluctuation in insulin and blood glucose compared to those with Type2 diabetes mellitus. He also claims that estimation of hemoglobin A1c can nullify the effects of patients consciously changing their diet on the day prior to the test. In this study we have specifically ensured that patients continue with their normal diet at the time of the test .Seshiah et al opined that for the same reason (viz. lesser fluctuation in insulin and blood glucose in Type 2 patients fasting blood glucose can be used as a relatively accurate indicator of overall metabolic control- Recently, an Italian study by Veglio et al conducted on 221 Type 2 patients hemoglobin A1c was highly significantly correlated with the fasting blood glucose value ($p=<0.0001$).. The extensively researched marker, currently in use for the long term monitoring of the glycemic status among diabetics, is the Glycated hemoglobin test. Whereas all the other tests measuring glucose indicates only the immediate Glycemic status , Glycated hemoglobin (GHb) is the only test that gives the measure of mean blood glucose (MBG) “round the clock” for the last 2-3 months. The approximate mapping between

HbA1c values and estimated average blood glucose measurements is given by the following equation:[60]

$$\text{eAG(mg/dl)} = 28.7 \times \text{A1C} - 46.7$$

$$\text{eAG(mmol/l)} = 1.59 \times \text{A1C} - 2.59$$

Data in parentheses are 95% CIs.

Control of fasting hyperglycemia is necessary but usually insufficient for achieving HbA1c goals <7%. Control of postprandial hyperglycemia is essential for achieving recommended HbA1c goals.[62]

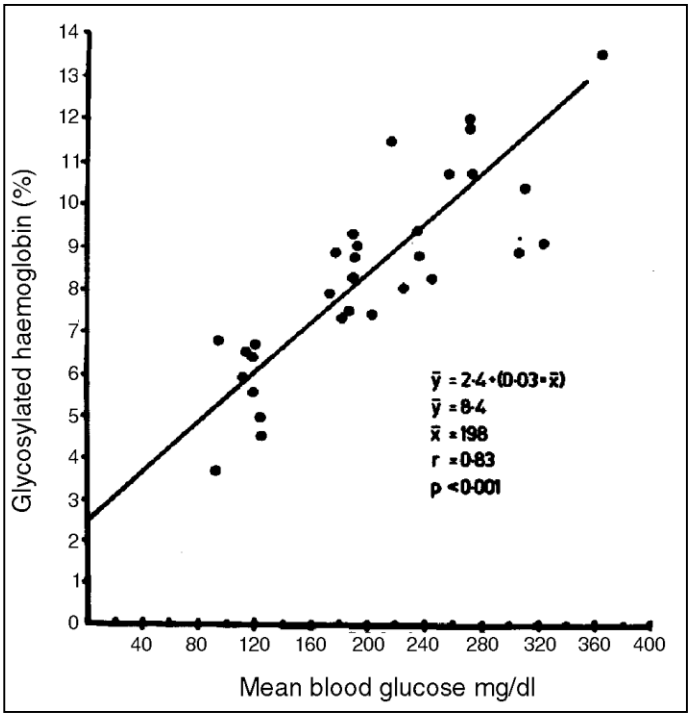
Three levels of glycemic control, namely, good ($HbA_{1c} \leq 7\%$)/ mpg 170mg%, fair ($HbA_{1c} > 7–9\%$)/mpg170-240mg%, and poor ($HbA_{1c} > 9\%$) /mpg>240mg%have been recognised.

Of interest, in patients with diabetes, the prandial glucose level is more strongly correlated with HbA1c than is the fasting glucose level.[61]

CORRELATION BETWEEN HBA1C LEVEL AND MEAN PLASMA GLUCOSE LEVELS ON MULTIPLE TESTING OVER 2–3 MONTHS

HbA1C (%)	Mean plasma glucose	
	mg/dl	mmol/l
6	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5
11	310	17.5
12	345	19.5

RELATIONSHIP OF MEAN BLOOD GLUCOSE AND GLYCOSYLATED HAEMOGLOBIN.



METHODS :

CARDIOVASCULAR TESTS

Seven cardiovascular autonomic tests were done to assess both sympathetic and parasympathetic function. Four tests evaluating parasympathetic, two tests evaluating sympathetic and one test evaluating both parasympathetic and sympathetic function. These tests are:

1. Deep breathing test
2. Heart rate response to standing
3. Heart rate response to valsalva manouvre
4. Heart rate response to intravenous atropine
5. Blood pressure response to standing
6. Blood pressure response to sustained hand grip
7. Squatting test

All ECGs were recorded in BPL Cardiart 108T/MK-vl ECG machine

1. DEEP BREATHING TEST

To assess heart rate response to deep breathing at six cycles per minute, the patient sits quietly and is connected to ECG machine. The patient is instructed to breathe deeply and evenly at six breaths per minute (Five seconds in and five seconds out). The heart rate was recorded in lead II simultaneously with ECG machine.

The maximum and the minimum heart rates during each 10 sec breathing cycle are measured and the mean of the differences for three successive breathing cycles gives the heart rate variation. A variation score of 9 or less is abnormal. Another way to express heart rate changes is the ratio of the longest R-R interval during expiration to shortest R-R interval during inspiration, the E:I ratio.[33]

In this study the heart rate change is expressed as EI ratio. It is calculated as follows:—

$$EI\ ratio = \frac{Mean\ of\ longest\ R-R\ interval\ during\ expiration}{Shortest\ R-R\ interval\ during\ inspiration}$$

2. 30^{th} /15^{th} RATIO TEST.

To assess heart rate response to standing up from lying position. The subject is asked to lie quietly on a couch and then to stand up unassisted, tracing are recorded in lead II with ECG machine continuously during standing up time for more than 30 beats. The $30/15^{th}$ ratio is calculated as follows:-

$$\frac{30}{15} Ratio = \frac{The\ longest\ R-R\ interval\ around\ 30th\ beat}{The\ shortest\ R-R\ interval\ around\ 15th\ beat}$$

3.VALSALVA MANOUEVRE.

To assess heart rate response to Valsalva manouevre. The technique involves the subjects to blow into a mouth piece connected to a manometer up to 40 mm of Hg pressure for 15 sec and asked to stop blowing. A continuous ECG is recorded in standard lead II during the st raining period and immediately after the release of pressure for 30 sec. The valsalva ratio is calculated as follows-

$$Valsalva\ Ratio = \frac{longest\ R-R\ interval\ immediately\ after\ the\ manoeuvre\ (with\ in\ about\ 20\ beats)}{shortest\ R-R\ interval\ during\ the\ manoeuvre}$$

4.HEART RATE RESPONSE TO INTRAVENOUS ATROPINE

This test was carried out by injecting 1.8mg of atropine sulphate by slow IV route. The ECG is recorded in standard lead II during rest before injection when the subject is lying quietly and three minutes after IV atropine.

The difference in heart rate is expressed as a ratio and is calculated as follows (Gulati,1980)[54] :

$$Heart\ rate\ Response\ to\ Atropine = \frac{Longest\ R-R\ interval\ during\ rest}{shortest\ R-R\ interval\ after\ Iv\ atropine}$$

5. POSTURAL BLOOD PRESSURE TEST

This is a simple test to measure the integrity of sympathetic pathway. Blood pressure was measured with the patient in supine position and after standing for 2 min.

A decrease in systolic blood pressure of 20mm of Hg or more and / or a fall in diastolic pressure grater than 10mm Hg upon standing is abnormal.[8]

6. BLOOD PRESSURE RESPONSE TO SUSTAINED HAND GRIP

This test was performed in this study as follows;-

The subjects were asked to maintain handgrip at 30% of maximum voluntary contraction upto 5min. Using aneroid manometer, the blood pressure was measured each minute.

The difference between the diastolic blood pressure just before the release of handgrip and before starting is taken as the measure of response.

7. SQUATTING TEST

In this study standard squatting test was performed while a continuous ECG was recorded in lead II. Also subjects were instructed to refrain from smoking and drinking coffee on the test day. Each subject stood still for 3min (Phase I) and then squatted 1min. (Phase II). Lastly, each patient stood up during inspiratory phase and

remained in the standing position for 1min (Phase III) The squatting induced heart rate changes was expressed by SqT vagal ratio (SqTv) and SqT sympathetic ratio (SqTs) which are calculated as follows.

$$SqTv = \frac{Base\ line\ R-R\ interval\ during\ phase\ I\ (mean\ of\ 10\ beats\ just\ before\ squatting)}{Longest\ R-R\ interval\ in\ the\ first\ 15\ \text{sec}\ of\ phase\ II}$$

$$SqTs = \frac{Base\ line\ R-R\ interval\ during\ phase\ I}{shortest\ R-R\ interval\ in\ the\ first\ 10\ to\ 20\ \text{sec}\ of\ phase\ II}$$

The results are interpreted with reference to normal ranges for SqT ratio's in normal subjects of 20 - 74 years of age (Marfella R et al, 1974)[38] as shown in this table. Normal ranges for SqT ratios in normal subjects 20—74 years of age.

Age (years)	n	SqTs ratio (CI)		SqTv ratio (CI)	
		Lower 95%	Lower 99%	Higher 95%	Higher 99%
20-24	56	1 .55	1.54	0.50	0.61
25-29	53	1.47	1.46	0.61	0.62
30-34	67	1 .43	1.42	0.63	0.64
35-39	42	1.36	1.34	0,66	0.67
40-44	54	1.32	1.31	0.71	0.72
45-49	40	1.29	1,28	0.73	0.74
50-54	48	1 .26	1.24	0.77	0.78
55-59	60	1 .20	1.19	0.82	0.83
60-64	53	1 .15	1.14	0.86	0.87
65-69	45	1.10	1.09	0.89	0.90
70-74	40	1 .07	1.06	0.92	0.93

Abnormal values are less than the lower 99% CI (Confidence Interval) for SqTs ratios and greater than the Higher 99% CI for SqTv ratios.

INTERPRETATION OF TEST RESULTS

Name of the test	Normal	Borderline	Abnormal
Valsalva ratio	≥ 1.21	1.11 – 1.20	≤ 1.10
EI ratio*	≥ 1.21	1.11 – 1.20	≤ 1.10

30/15 ratio*	≥ 1.04	1.01 – 1.03	≤ 1.00
IV atropine test**	≥ 1.21	1.11 – 1.20	≤ 1.10
'Decrease in systolic pressure on standing*	≥ 10 mm of Hg	11-19 mm of Hg	≤ 20 mm of Hg
Increase in Diastolic Pressure after sustained handgrip*	≥ 16 mm of Hg	11-15 mm of Hg	≤ 10 mm of Hg

'Reference - : * Ewing [53]** Gulati[54]

RESTING TACHYCARDIA

Recorded by palpatory method and confirmed by ECG recordings.

BODY MASS INDEX

Body mass index BMI was calculated for each patient using the formula

$$BMI = \frac{Weight\ in\ kg}{Height\ in\ m2}$$

.

ULTRASONOGRAM ABDOMEN

Ultrasonogram was performed to rule out renal calculus, enlargement of prostate and to measure the kidney size.

Duration of diabetes, type of treatment and family history of diabetes were derived from the patient's history and file.

BIOCHEMICAL TESTS

The following are the Biochemical tests carried out in this study.

≠ Fasting Blood Sugar.

≠ Post Prandial Blood Sugar 2 hr. after 75gm of Glucose load.

≠ Blood Urea.

≠ Serum Creatinine,

≠ Serum Cholesterol.

≠ Hemoglobin

≠ 24 hrs Urinary Protien.

Statistical association was calculated by using Chi-Square test.

ANALYSIS OF RESULTS

General characteristics.

This study was conducted on 40 diabetic patients including 4 newly detected diabetic patients- 65% were males and 35% were females. The age distribution of population studied ranged from 40 to 79 years. Their mean age was 55.37 ± SD 10.3 years. The mean duration of diabetes was 5.00 ± SD 4.99 years. The mean fasting and post-prandial blood glucose level was 186 ± SD 55.45 mg% and 247 ± SD 54.87 mg% respectively. The mean body mass index was 21.5 ± SD 4.2, the mean 24 hr urine protein was 372 mg and the mean cholesterol was 194.9 ± SD 35.2 mg%.

10 healthy volunteers were studied as controls (6 males and 4 females). Their mean age was 51.5 ± SD 9.25 and BMI was 21.2 ± SD 2.3. The mean fasting and post-prandial blood sugar values were 83 ± SD 9.05 mg% and 98.4 ± SD 11.7 mg%respectively. The mean 24 hr urine protein was 90.2 ± SD 3.9 mg. The mean cholesterol was 189 ± SD 11.93 mg%. No one in the control group had abnormal cardiovascular function tests.

ANALYSIS OF SYMPTOMS

The distribution of symptoms and signs of autonomic neuropathy and other characteristics are shown in table B.

1. Postural hypotension

Out of 40 diabetics studied 26 (65%) persons had symptoms of postural hypotension. Out these 14 were males and 12 were females. The incidence of postural hypotension in males and females were 53.8% and 85.7% respectively ($p<0.01$). This suggests that in diabetics female sex is associated with greater incidence of postural

hypotension. Out of 26 patients with postural hypotension only 9 (34.6*4) patients had systolic fall of blood pressure more than 20 mm of Hg upon standing and 11 (42.6%) patients had borderline systolic blood pressure fall. This suggests that 6 patients who had the symptom with normal systolic blood pressure fall upon standing may be due to other causes .

The average age of diabetic patients with postural hypotension was 56 years and the average duration of diabetes was 5.46 years. The average fasting blood sugar value was 205 mg% and the average post prandial blood sugar value was 258 mg% suggesting that most of the people with this symptom had poor control of diabetes.

2. Gastric fullness

The total number of patients presented with this symptom were 30 (75%) among which 16 were males and 14 were females; out of 26 male diabetics studied only 16(<61.5%) had gastric fullness whereas all the 14 (100%) ($p<0.01$) females studied had this symptom. This suggests that association of gastric fullness is more common in females with diabetes than males.

The average age of diabetics with this symptom was 55 years and the average duration was 5.53 years. All the patients had poor control of the disease with average fasting and post prandial blood sugar values 197 mg% and 252 mg % respectively.

3. Nocturnal diarrhoea

Nocturnal diarrohea was present in only 4 (10%) persons out of 40 diabetic subjects studied. The incidence of this symptom was 7.7% for males and 14.3% for females ($p<0.01$) suggesting that females with diabetic autonomic neuropathy have greater association with this symptom than males.

The average age and duration of diabetes was 59 years and 5 years respectively. The average fasting blood sugar was 252 mg% and post prandial blood

sugar value was 305mg%. The degree of control of diabetes was poor in all these patients.

4. Urinary symptoms

Urinary symptoms such as diminished sensation of bladder fullness, hesitation, weakness of stream and overflow incontinence were present in 10 (25%) patients with autonomic neuropathy of which 7 were males and 3 were females. The incidence of urinary symptoms in males and females was 26.9% and 21.4% (p).

The average age of patients with urinary symptoms was 54 and the average duration was 7.5 years. The average fasting and post prandial blood sugar values are 201 mg% and 253 mg% respectively. This suggests that diabetics with longer duration of disease and poor control of their blood sugar level are likely to develop urinary symptoms.

5. Impotence

Out of 26 diabetic males studied 17 (65.4%.) of them had impotence. The average age of people with this symptom was 59 and the average duration was 3.56 years and the average fasting blood sugar value was 195 mg%, the average post prandial blood sugar value was 259 mg%. Occurrence of impotence in males with diabetic autonomic neuropathy is not associated with duration of the disease whereas the association is greater with increasing age and poor degree of control.

Out of 17 patients with impotence 11 (64.7%) had abnormal deep breathing test 9 (52.97%) had abnormal 30th/15th test and other parasympathetic function test were abnormal in less than 40%. Among the 17 patients with impotence, 3 (17.6%) had abnormal postural blood pressure test and 4 (23.5%) had abnormal handgrip test.

6.Disturbance of sweating

Overall 30 (75%) diabetic patients with autonomic neuropathy had sweating abnormality. Among these patients 18 (69.5%) were males and 12 (85.7%) were females. The average age and duration of diabetes was 53 years and 5.4 years respectively. The average fasting and post prandial blood sugar values were 194 and 258 respectively.

Out of 30 patients with abnormality of sweating 22 (73.3%) patients had abnormal deep breathing test and 19 (63.3%) had abnormal 30th/15th ratio test. Other test for parasympathetic function were abnormal in less than 50%. Among the patients with this symptom 8 (26.7%) had abnormal postural blood pressure test and 9 (30%) had abnormal handgrip test.

It was observed that patients with longer duration of diabetes and poor degree of glycemic control are likely to have greater association with sweating abnormality. Both parasympathetic and sympathetic tests were found abnormal particularly the deep breathing test ,30th/15th test and handgrip test.

7.Tingling and numbness

Out of 40 subjects studied 32 (80%) had tingling and numbness, 20 (76.9%) patients were males and 12 (85.7%) patients were females. The average age and duration of diabetes was 50 years and 5.22 years respectively. The average fasting blood sugar was 198 mg% and post prandial blood sugar value was 261 mg%. Out of 32 patients with this symptom 22 (68.5%) and 21 (65.6%) had abnormal deep breathing and 30th/15th ratio tests,53% had abnormal valsalva manoeuvre and 12.5% had abnormal atropine test. The postural blood pressure test and hand grip test were found to be abnormal in 9 (28.5%) and 11 (34.9%) respectively.

The results suggest greater association of this symptom with increasing age and poor control. The cardiovascular function tests, more likely to be abnormal are deep breathing test , 30th/15th ratio test and handgrip test.

8.Tendon reflexes

All the patients studied were tested for presence or absence of both ankle and knee jerks. Ankle jerk was absent in 16 (40%) of patients. Among them 10 (38.5%) were males and 6 (42%) were females. Among the patients with absent ankle jerk the deep breathing test was abnormal in 75%, the 30th/15 test in 63.8%,the valsalva test in 50% and other tests including sympathetic function tests were abnormal in less than 30% of patients. The knee jerk was abnormal in 5 (12.5%) patients with autonomic neuropathy; out of these 2 were males and 3 were females.

In patient with absent knee jerk the average age and duration was 50 years and 5.6 years respectively and the average fasting and post prandial blood sugar values were 188 mg% and 243 mg% respectively. Deep breathing test was abnormal in 60% and all other parasympathetic tests and handgrip test were abnormal in 40% patients.

In patients with absent ankle jerk the average duration and age, fasting and post prandial blood sugar values were 6.38 years, 57years, 188 mg% and 247 mg%respectively. Out of 16 patients, 12 (75%) had abnormal deep breathing test, 11 (68.8%) had abnormal 30th/15th test. All other tests were abnormal in less than 26% of patients.

Out of 21 patients with absent tendon reflexes 5 had both knee and ankle jerks absent. Right lateral popliteal motor nerve conduction velocity was delayed in 12 patients out of 16 patients with absent ankle jerk and right median nerve motor nerve conduction velocity was delayed in 3 patients with absent knee jerk. The association

of absent tendon reflexes is likely to be greater in patients with autonomic neuropathy with increasing age ,increasing duration of diabetes and with poorly controlled diabetes.

9.Eye changes

Out of 40 patients studied 4 (10%) had cataract and 3 (7.5%) had non proliferative diabetic retinopathy. The average duration of diabetes and age were 7 years and 61years respectively. The average fasting and post prandial blood sugar values were 173 mg% and 231 mg%. Deep breathing test was abnormal in 71.4% of patients and 30th/15th ratio test was abnormal in 42% of patients. Valsalva test was abnormal in 47.1% of patients. The IV atropine test and handgrip test were abnormal in 14.3% of patients.

Analysis of results showed that with increasing age and duration of diabetes and poor control there is greater association of development of retinopathy.

10. Resting tachycardia

Resting tachycardia was found in 13 (32.5%) patients out of 40 patients studied. The average age, duration, fasting and post prandial blood sugar values were 51 years, 6 years, 195 mg% and 267 mg% respectively.

92.5% of patients had abnormal deep breathing test, 84.6% of patients had abnormal 30th/15th ratio, 61.5% of patients had abnormal valsalva test and 7.7% of patients had abnormal atropine test.

RESULTS OF CARDIOVASCULAR FUNCTION TESTS

The results of cardiovascular tests are shown in the table C.

1.Deep breathing test (El-Ratio)

In this study El-Ratio was used to assess the parasympathetic dysfunction. Out of 40 subjects with diabetes of varying duration and age studied, the test was abnormal in 27 (67.5%) patients, borderline in 11 (27.5%) patients and normal in 2 (5%) patients, the distribution of abnormality was approximately same in males and females. The average age, duration, fasting and post prandial blood sugar values for patients with abnormal test were 54 years, 5.4 years, 197 mg%, 257 mg% respectively.

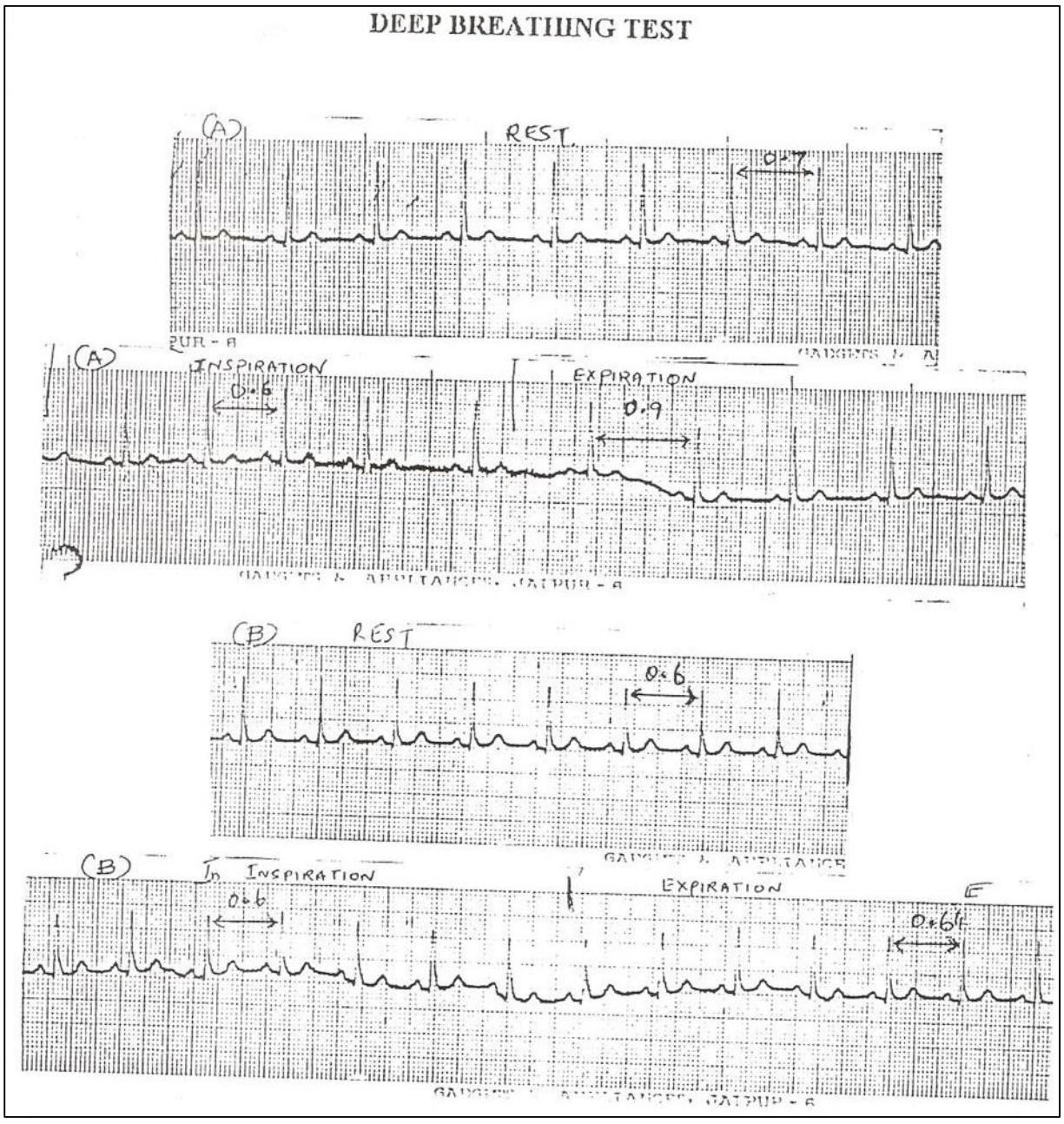
It was observed from this study that patients with abnormal deep breathing test had longer mean duration of the disease and higher mean fasting and post prandial blood sugar values when compared to patients with normal test. Age doesn't correlate with positive test result.

2. Heart rate response to getting up from lying to standing (30th/15th ratio)

This test is used to assess parasympathetic abnormality. A total of 23 (57.5%) patients found to have abnormal 30th/15th ratio test. In 17 (42.5%) patients the test was found to be normal. Out of 23 patients with abnormal test 13 (50%) were males and 10 (71.4%) were females. In the normal group there were 17 patients. 13 (50%) were males and 4 (28.6) were females. In patients with abnormal test the average age was 54 years and the average duration of diabetes was 5.1 years. The average fasting and post prandial blood sugar values were 201 mg% and 265 mg% respectively, whereas in patients with normal test the average age ,duration, fasting and post prandial blood sugar values were 59 years,4.8 years,166 mg%,223 mg% respectively.

The results of this test shows that in diabetes with autonomic neuropathy females are more likely to have positive 30th/15th ratio test and there is a greater association of positive test with increasing age, duration and degree of metabolic control.

Deep breathing test: ECG recordings showing R-R intervals during inspiration and expiration in (A) normal person. (B) Diabetic patient with autonomic neuropathy.



3. Valsalva manoeuvre

Overall 18 (45%) patients had abnormal valsalva test,15 (37.5%) patients had borderline test and 7 (17.5%) had normal test results. The sex distribution of abnormal test was more or less same. The average age, duration, fasting and post prandial values for the abnormal group were 54 years,7.1 years, 205 mg% and 259 mg% respectively and for the normal group the values were 55 years,2.9 years,167mg%,231 mg% respectively.

Valsalva manoeuvre: ECG recordings showing R-R intervals during and immediately after the procedure in (A) Normal person. (B) Diabetic patient with autonomic neuropathy.

It is observed that increasing duration and poor degree of control of diabetes have positive correlation with abnormal test result. Age does not correlate with abnormality.

4. IV Atropine test

Only 5 (12.5%) out of 40 patients were found to have abnormal atropine test. 55% of test population had normal test response to atropine and 37% had borderline test response.61.5% of males and 42.3% of females had normal response,30.8% of males and 35.7% of females had borderline response to atropine and 7.7% of males and 21.4% of females had abnormal test response respectively. The average age, duration, fasting and post prandial sugar values for the abnormal group were 50 years,4.6 years,245 mg% and 301 mg% respectively. In the normal group the average age, duration and fasting and post prandial sugar values were 55 years, 3.9 years,166 mg% and 235 mg% respectively. In this test also there exist positive correlation with poor degree of control of diabetes and duration when compared to normals. Age does not show any positive correlation with abnormality of the test.

5.Postural blood pressure test

Analysis of postural blood pressure test results showed incidence of abnormal test was 25% and the male to female distribution was 19.2% and 35.7% respectively. Out of 40 test population 35% had borderline response to standing from lying, among these 30.8% were males and 42.9% were females. 40% of patients fall under normal group .In normal test group the male to female distribution were 50% and 21.4% respectively. The average age, duration of diabetes, fasting and post prandial blood sugar values in patients with abnormal test were 60 years,6.8 years,209 mg% and 259 mg% respectively and in normal test group were 55 years,4.1 years,172 mg% and 240 mg% respectively.

In this study it was observed that increasing age, duration of diabetes and poor degree of control have strong influence on postural blood pressure test. This test was abnormal in only 9 patients out of26 patients with symptom of postural hypotension.

6. Sustained handgrip test

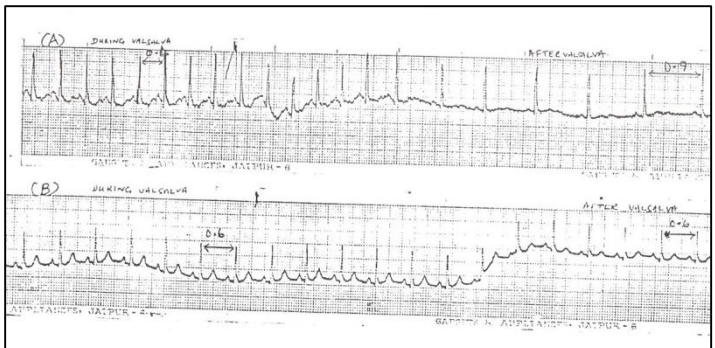
Out of 40 patients studied 30% were found to have abnormal increase in diastolic blood pressure more than 16 mm of Hg. of which male to female distribution was 23.1% and 42.9% respectively.62.5% of test population had normal increase in diastolic blood pressure of which 73.1% were males and 42.9% females. 7.5% fall under borderline group among them 3.8% were males and 14.3% were females. The average age, duration, fasting and post prandial blood sugar values in normal test population were 56 years,3.4years,168 mg% and 234 mg% respectively and the average values in abnormal test population was 54 years, 8.5 years, 218mg% and 276 mg% respectively.

This test is used to assess sympathetic function. Those patients with abnormal test were considered to have sympathetic damage. Poor degree of control of the disease and longer duration disease have greater association with abnormality of this test.

7. Squatting test

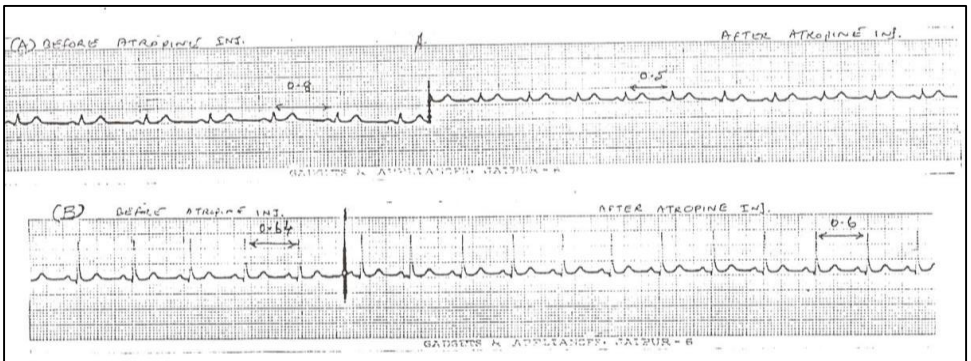
Both sympathetic and parasympathetic dysfunction may be assessed with this single test. In this study all the 40 subjects studies were found to have abnormal Sq T – Vagal ratio and 37 out of 40 patients had abnormal Sq T – Sympathetic ratio and 3 had normal sqt -sympathetic ratio

valsalva manoeuvre



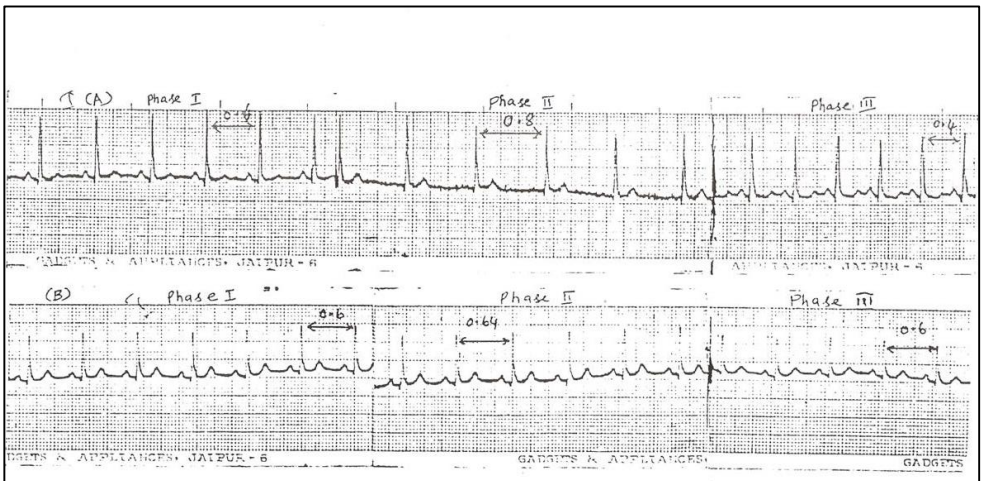
Valsalva manoeuvre : ECG recordings showing R-R intervals during and immediately after the procedure in (A) Normal Person. (B) Diabetic patient with autonomic neuropathy.

IV ATROPINE TEST



Iv atropine test : ECG recordings showing R-R intervals before and after the injection in (A) Normal person. (B) Diabetic patient with autonomic neuropathy.

SQUATTING TEST



Squatting test : ECG recording showing R-R intervals during phases, I, II, III in (A) Normal person. (B) Diabetic patient with autonomic neuropathy.

ANALYSIS OF GRADING OF DYSAUTONOMIA

Grading of severity of autonomic neuropathy was done according to lakotia et al, 1997.[55]

Grading of dysautonomia according to Lakotia et al 199755

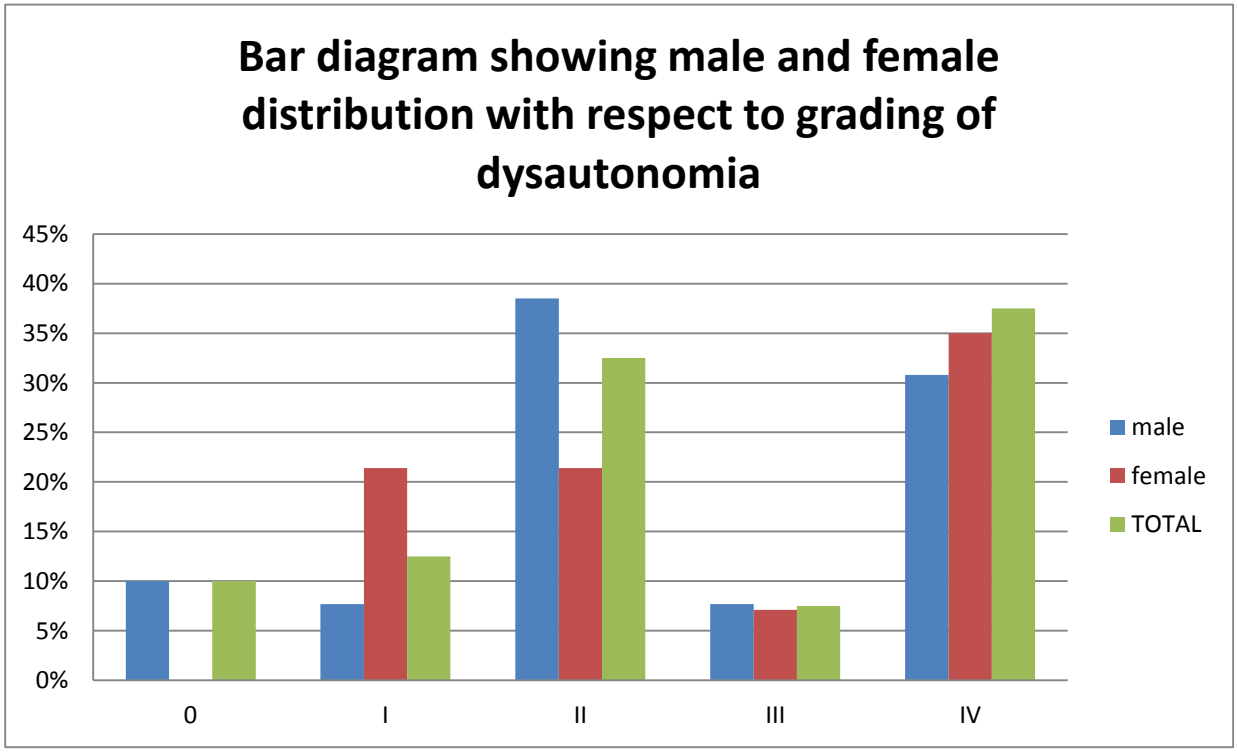
Grade	Severity	Result of parasympathetic tests	Result of sympathetic tests
0	Normal sympathetic and parasympathetic functions	All normal or one Borderline	Normal
I	Mild parasympathetic dysautonomia	One abnormal or two borderline	Normal
II	Moderate parasympathetic dysautonomia	Two abnormal or one abnormal and two borderline	Normal
III	Severe parasympathetic dysautonomia	More than two abnormal results	Normal
IV	Combined parasym- pathetic and sympathetic dysautonomia	Any parasympathetic abnormality	One abnormal or two borderline

Distribution of grades of dysautonomia in the study population and its relations to age, duration of the disease, metabolic control, symptoms and signs, body mas index, proteinuria, serum cholesterol and type of treatment are shown in tables.

DISTRIBUTION OF VARIOUS GRADES IN THE POPULATION STUDIED.

Table D

Grade	Male	Female	Total	Fasting Blood Sugar	Post. Prandial Blood Sugar
0	4 (10%)	0	4 (10%)	158	225
I	2 (7.7%)	3 (21.4%)	5 (12.5%)	166	229
II	10 (38.5%)	3 (21.4%)	13 (32.5%)	172	238
III	2 (7.7%)	1 (7.1%)	3 (7.5%)	193	257
IV	8 (30.8%)	7 (35%)	15 (37.5%)	211	264



This above bar diagram shows increased incidence of grade 4 dysautonomia in both male and female diabetic population.

DISTRIBUTION OF AGE IN RELATION TO DYSAUTONOMIA

Table E

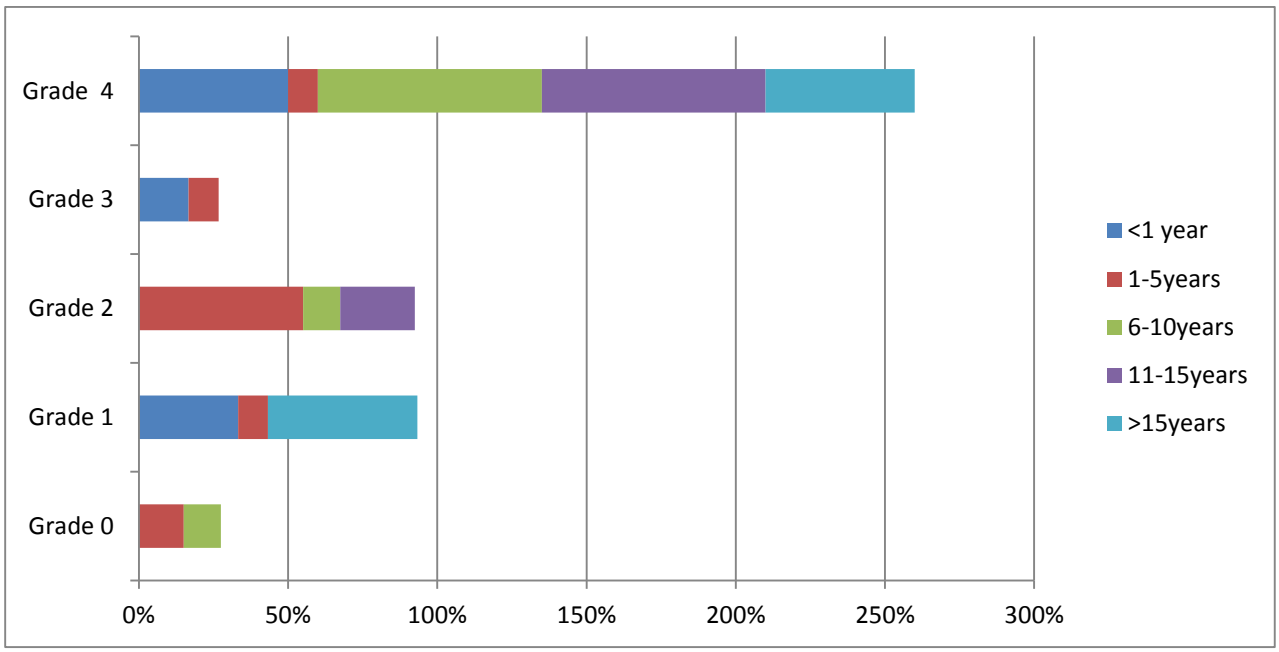
Age Group	Total No	Grade 0	Grade I	Grade II	Grade III	Grade IV
40 - 50	16 (40%)	-	3 (8.8%)	4 (25%)	2(12.5%)	7(43.5%)
51 - 60	14 (35%)	2(14.3%)	-	5(35.7%)	1 (7.1%)	6(42.9%)
61 - 70	6 (15%)	2(33.3%)	1 (16.7%)	2 (33.3%)	-	1(16.7%)
71 - 80	4 (10%)	_	1 (25%)	2 (50%)	-	1 (25%)
Total	40 (100%)	4 (10%)	5 (12.5%)	13(32.5%	3 (7.5%)	15 (75%)

This table shows the distribution of age in the study group in relation to the grades of dysautonomia .

GRADING OF DYSAUTONOMIA AND ITS RELATION TO DURATION OF DIABETES. DURATION IN YEARS AND TOTAL NOS. IN EACH GRADE AND PERCENTAGE

Table F

Duration	Total No	Grade 0	Grade I	Grade II	Grade III	Grade IV
< 1 year	6 (15%)	_	2(33.3%)	-	1 16.7%)	3 (50%)
1 – 5	20 (50%)	3 (15%)	2 (10%)	11 (55%)	2 (10%)	2 (10%)
6-10	8 (20%)	1(12.5%)	-	1(12.5%)	-	6 (75%)
11 – 15	4 (10%)	-	-	1 (25%)	-	3 (75%)
>15 years	2 (5%)	-	1 (50%)	-	-	1 (50%)
Total	40 (100%)	4 (10%)	5(12.5%)	13(32.5%	3 (7.5%)	15 (75.5%

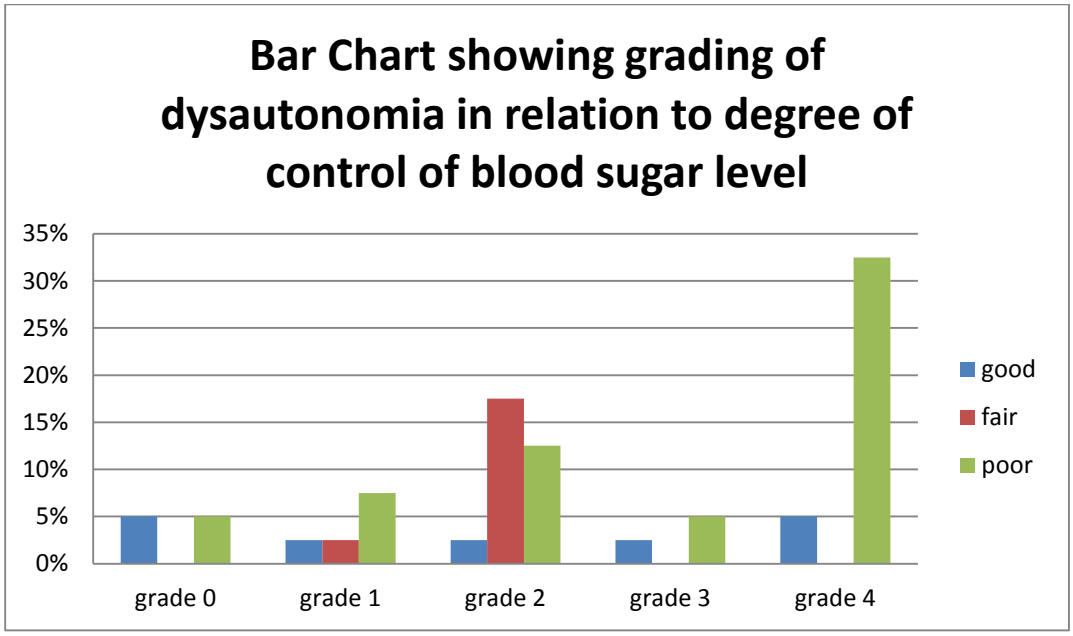


This above chart shows increase in incidence of grade 4 dysautonomia in the population with greater than 10years of duration of diabetes mellitus .

GRADING OF DYSAUTONOMIA AND ITS RELATION TO DEGREE OF CONTROL ACCORDING TO FASTING BLOOD SUGAR LEVEL. TOTAL NOS. IN EACH GROUP AND THE PERCENTAGE. p value<0.01%

Table G.

Degree of Control	Total No	Grade 0	Grade I	Grade I I	Grade I I I	Grade IV
Good	7 (17.5%)	2(5 %)	1(2.5%)	1 (2.5%)	1 (2.5%)	2(5 %)
Fair	8 (20%)	-	1 (2.5%)	7(17.5%	-	-
Poor	25(62.5%)	2(5 %)	3(7.5%)	5(12.5%	2(5 %)	13(32.5%
Total	40 (100%)	4 (10%)	5(12.5%)	13(32.5%	3 (7.5%)	15(35.5%

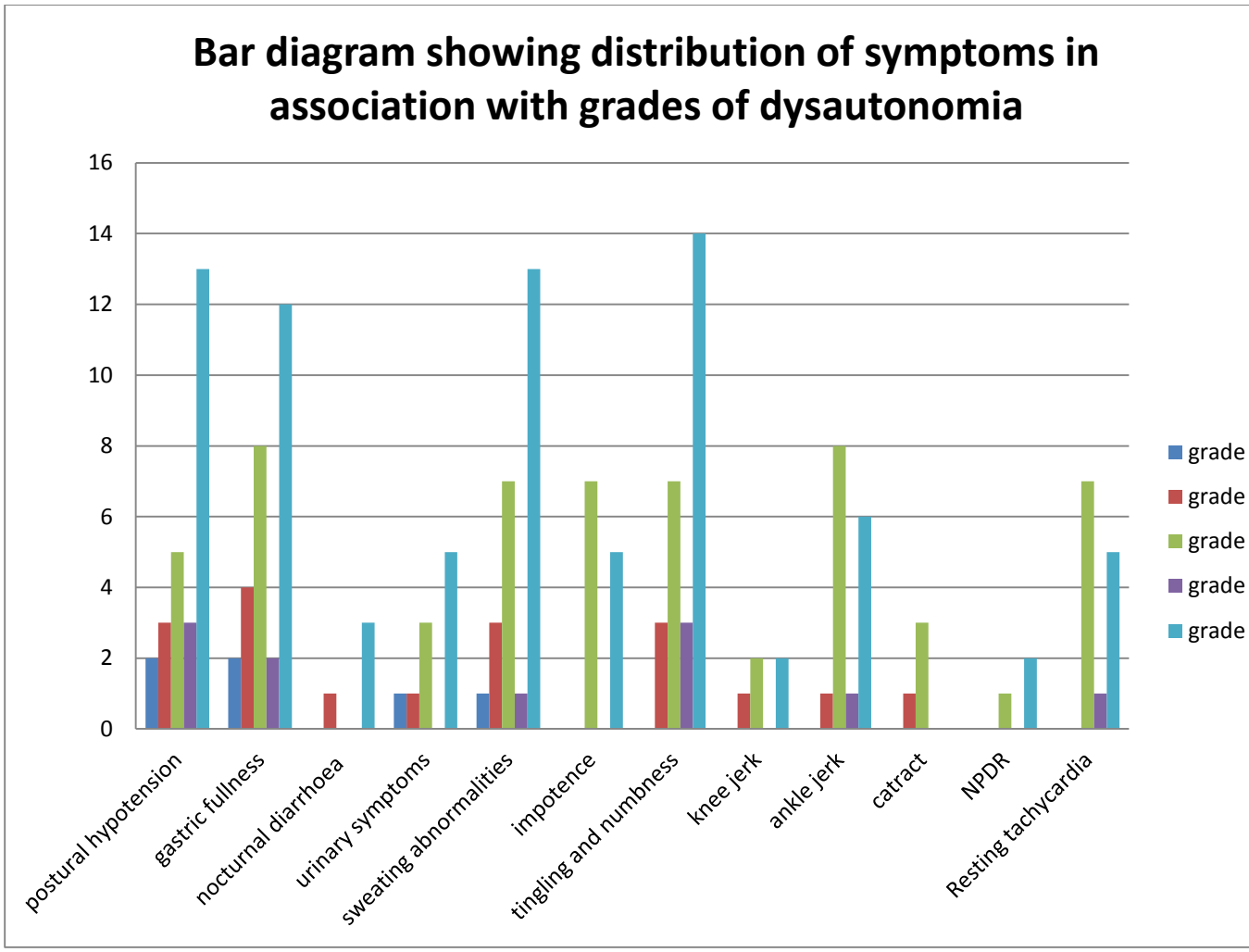


This chart shows increased prevalence of grade 4 dysautonomia in the population with poorer glycemic control .

DISTRIBUTION OF NUMBER OF PATIENTS IN EACH GRADE ACCORDING TO AUTONOMIC SYMPTOMS.

Table H.

Symptom	Total Nos.	Grade 0	Grade I	Grade II	Grade III	Grade IV
Postu. Hypot.	26 (65 %)	2	3	5	3	13
Gast. Fulnes	28 (70 %)	2	4	8	2	12
Noct. Diarr.	4 (10 %)	0	1	0	0	3
Urina. Symp.	10 (25 %)	1	1	3	0	5
Sweat. Abnor.	25 (62.5%	1	3	7	1	13
Impot.	14 (35%)	2	0	7	0	5
Ting1. Numbn .	28 (70 %)	1	3	7	3	14
Knee Jerk	5 (12.5%	0	1	2	0	2
Ankle Jerk	16 (40 %)	0	1	8	1	6
Eye.Ch Catrac	4 (10 %)	0	1	3	0	0
Eye.ch NPDR	3 (7.5%)	0	0	1	0	2
Restig Tachyc	13 (32.5%	0	0	7	1	5



This above bar chart shows that there is increased prevalence of postural hypotension , gastric fullness , sweating abnormalities , paresthesias , resting tachycardia in the study group with grade 4 dysautonomia .

DISTRIBUTION OF GRADES OF DYSAUTONOMIA IN RELATION TO BODY MASS INDEX

Table J. **P > 0.05**

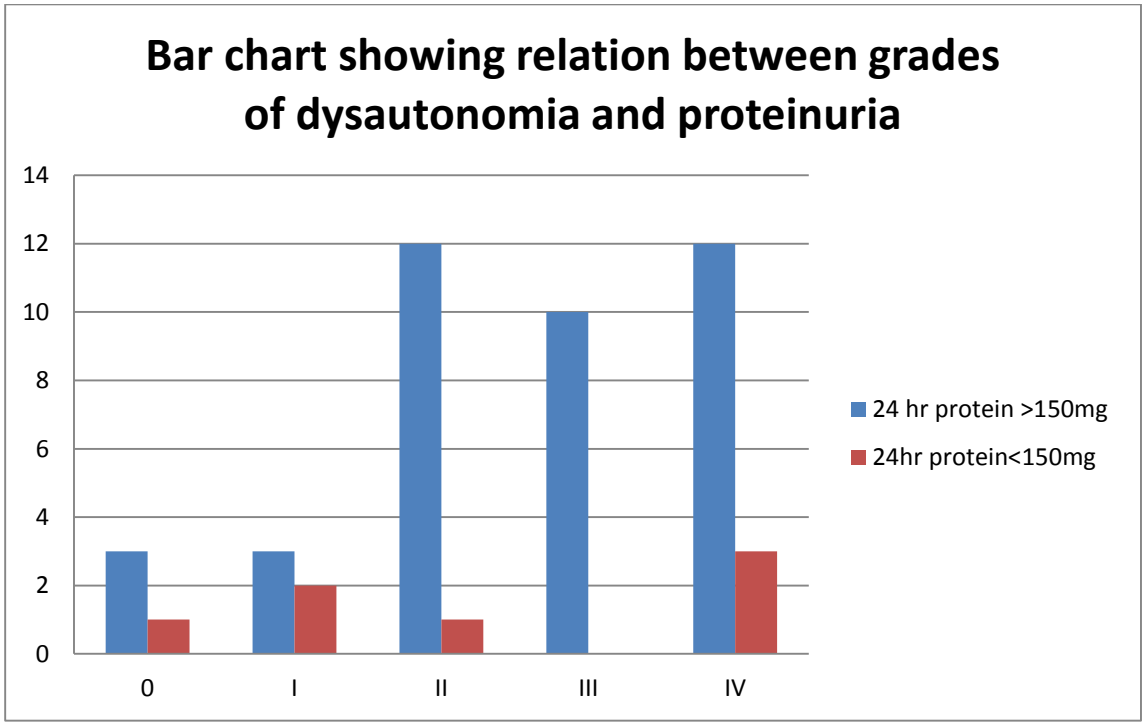
Grade	Over Wt .& Obese		Non Obese Nos.	%
0	1	25	3	75
I	3	60	o	40
II	1	7.7	12	92.3
III	0	0	3	100
IV	4	26.7	11	73.3

There was no statistically significant relation between the body mass index and dysautonomia .

DISTRIBUTION OF GRADES OF DYSAUTONOMIA ACCORDING TO PROTEINURIA

Table K. **P<0.01**

Grade	24 Hr Protein >150mg		24 hr Protein <150mg	
0	3	75	1	14.2
I	3	60	2	28.4
II	12	92.3	1	7.7
III	10	100	0	0
IV	12	80	3	20



This above chart shows that there is >150mg protein in urine /day in the study population with grade 2 and more than 2 dysautonomia

DISTRIBUTION OF GRADES OF DYSAUTONOMIA ACCORDING TO SERUM CHOLESTEROL

Table **L**. p>0.05

Grade	**Cholesterol ≥200mg**		**Choleterol < 200mg**	
	Nos.	**%**	**Nos.**	**%**
0	1	25	3	75
I	2	40	3	60
II	3	23.1	10	76.9
III	0	0	3	100
IV	6	40	9	60

There was no stastically significant correlation between levels of cholestrrol and grades of dysautonomia in this study .

DISTRIBUTION OF GRADES OF DYSAUTONOMIA ACCORDING TO TYPE OF TREATMENT.

Table M **P > 0.05.**

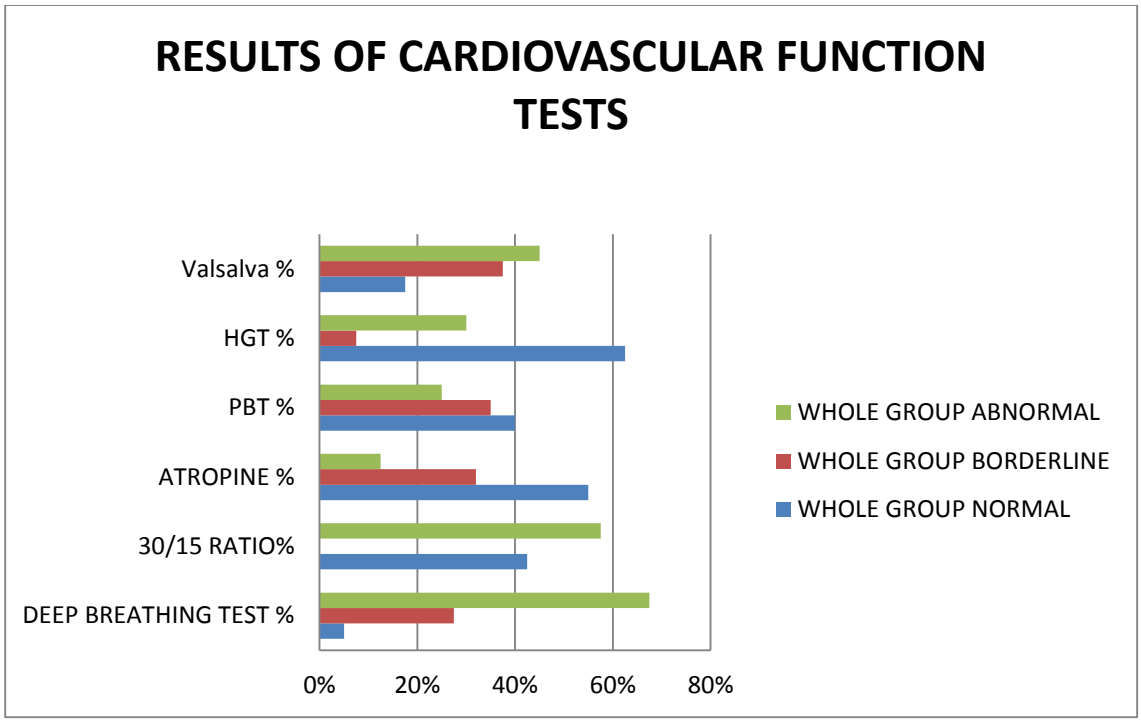
Grade	**OHA Alone Nos.**	**%**	**OHA And Insulin**		**Not on treatment Nos.**	
			Nos.	**%**		**%**
0	4	100	0	0	0	0
I	1	20	2	40	2	40
II	12	92.3	1	7.7	0	0
III	2	66.7	0	0	1	33.3
IV	11	73.3	3	20	1	6.7

There was no stastically significant correlation between the type of treatment and grades of dysautonomia in this study .

RESULTS OF CARDIOVASCULAR FUNCTION TESTS IN TYPE 2DM

GROUP	TEST RESULT	DEEP BREATHING TEST (n) %	30/15 RATIO(n)%	ATROPINE(n) %	PBT(n) %	HGT %	Valsalva Mano euvre
WHOLE GROUP	NORMAL	(2)5%	(17)42.50%	(22)55%	(16)40%	(25)62.50 %	7 (17.5%)
	BORDERLINE	(11)27.50%	(0)0%	(13)32%	(14)35%	(3)7.50%	15 (37.5%)
	ABNORMAL	(27)67.50%	(23)57.50%	(5)12.50%	(10)25%	(12)30%	18 (45%)
MALES	NORMAL	(2)7.60%	(13)50%	(16)61.50%	(13)50%	(19)73.10 %	4 (15.4%)
	BORDERLINE	(7)26.90%	(0)0%	(8)30.80%	(8)30.80%	(1)3.80%	11 (42.3%)
	ABNORMAL	(17)65.40%	(13)50%	(2)7.70%	(5)19.20%	(6)23.10 %	11 (42.3%)
FEMALES	NORMAL	(0)0%	(4)28.60%	(6)42.90%	(3)21.40%	(6)42.90 %	3 (21.4%)
	BORDERLINE	(4)28.60%	(0)0%	(5)35.70%	(6)42.90%	(2)24.30 %	4 (28.6%)
	ABNORMAL	(10)71.40%	(10)71%	(3)21.40%	(5)35.70%	(6)42.90 %	7 (50%)

This table shows that deep breathing test yielded more abnormal results in suggesting autonomic dysfunction.



this illustration shows that tests such as deep breathing tests are more yielding in detecting autonomic dysfunction.

DISCUSSION

This study was conducted on 40 Type2 diabetic patients- 65% of them were males and 35% females. The mean age of the population studied was 55.4 ± 10-3 years, and the mean duration of diabetes was 5.2 ± 5 years- The mean fasting and postprandial plasma glucose was 186 ± 55.45 mg% and 247 ± 54-87 mg% respectively. The majority of patients (40%) studied were in the age group of 40 - 60 years, (35 %) in the age group of 51-60 years, (15 %) of patients were in the age group of 61-70 years and (10 %) were in the age group of 71-80 years. The age of the population studied ranged from 40 to 79 years.

The duration of diabetes in most of the patients (50%) were in the group 1-5 years, 20 % of the patients were in 6 - 10 years group,10 % patients were in the 11 - 15 years group, 15 %of patients were in the <1 year group and only 2 (5 %) patients in the >15 years group. The disease duration in the population studied ranges from <1 years to 20 years.

Bulk of patitents (75 %) studied were on oral hypoglycemic drugs,15 % of patients were taking Insulin along with oral hypoglycemic agents and 10 % of patients who were newly detected as Type2 DM were not on any drugs. 50 % of the patients were on regular treatment and the rest were irregular in taking drugs. Most of the patients (62 %) were under poor degree of control of the disease with mean fasting and postprandial blood sugar value 219 ± 42.8 mg % and 272.88 ± 49.22 mg%, 20 % of the population studied were under fair control with mean fasting and postprandial blood glucose values 143 ± 6.12 mg% and 220 ± 33.23 mg% respectively. Only 17.5% were under good control with mean fasting and postprandial blood glucose values 117.7 ± 10.48 mg% and 185 ± 19.56 mg% respectively.

Autonomic involvement in diabetes mellitus has been widely studied earlier utilising non-invasive and invasive tests. It has been advocated that a battery of tests are better in detecting the autonomic involvement than single test done (*123,lakotia). In this study a battery of six

autonomic function tests were performed to assess the integrity of both sympathetic and parasympathetic function.

It has been found in this study that 33 (82.5%) of patients studied had one or more autonomic symptoms suggestive of autonomic neuropathy and 7 (17.5%) of population did not have any symptoms of autonomic impairment. Out of 33 patients 4 were established to have grade I dysautonomia,9 patients with grade II dysautonomia,3 with grade III dysautonomia and 15 were found to have grade IV autonomic neuropathy. Two patients were found to have normal autonomic function. In the symptomatic group 13 patients were found to have grade II autonomic damage and one was found with grade I dysautonomia. Two patients were found to have normal autonomic function and none of the patients were in grade III or IV group. Among the seven asymptomatic patients, five had evidence of dysautonomia on testing.

The presence of common symptoms such as impotence, postural dizziness and gustatory sweating [3,47] which are commonly seen in diabetes do not essentially mean damage to the autonomic nervous system. In this study out of 26 patient who complained of postural dizziness only 34.6% had abnormal fall in systolic blood pressure 20 mm of Hg. The complaint of postural dizziness may be due to other causes.

According to Ewing DJ. Et all (1930)[3] the presence of diabetic diarrhea almost always indicates severe autonomic damage. In our study four patients had diabetic

diarrhoes and all of them were found to have severe autonomic dysfunction (grade IV). Out of 40 diabetic subjects 10 (25%) patients complained of symptoms suggestive of involvement of bladder, of which 9 (90%) had abnormal parasympathetic function tests and 5 had abnormal sympathetic tests. This is in agreement with frimodt et all (1980) [56] who described that infrequently seen symptoms like dysphagia or abnormal bladder are also indicative of widespread autonomic damage.

A study of the various tests of autonomic functions showed that 82% patients had parasympathetic system involvement where as only 37.5% had sympathetic involvement in the subjects studied. This observation is in agreement with that of Ewing DJ. et.al al[29] and Banister R.[57]who suggested that sympathetic involvement in the course of diabetic autonomic neuropathy occurs later than parasympathetic involvement.

Among the individual tests of parasympathetic function, the greatest proportion of abnormal responses was seen in the deep breathing test (Beat to beat variation in the heart rate) in 27 patients (75 %). This is followed by the lying to standing test (30th/15th Ratio) in 23 patients (63.8 %), and finally the atropine test 5 patients (13.8 %).Among the sympathetic tests the incidence of abnormality was 27.7 % with sustained hand grip test and 33.3 % with postural blood pressure test. This suggests that in clinical practice the deep breathing test and the hand grip test may be the most easily observable and reproducible tests to evaluate the abnormalities of parasympathetic and sympathetic function respectively.

The novel squatting test described by marfella et al[38] combines both sympathetic and parasympathetic assessment in diabetic autonomic neuropathy in a single procedure. In our series 100 % patients had abnormal

parasympathetic component of the squatting test. It is relevant to note that even among 4 patients who had normal autonomic function according to the criteria of Lakotia et al the responses to squatting test was abnormal. It has been suggested by Marfella et al[38] that the squatting test may be the earliest indicator of diabetic autonomic neuropathy. All patients tested in our study had an abnormal squatting test response, even among those who had no other evidence of diabetic autonomic neuropathy.

In this study the severity of autonomic impairment was categorized as Grade 0 (Normal) - Grade IV (Severe) according to the criteria proposed by Lakotia et al (1997).[55]

According to this classification 90 % of patients out of a total of 40 were found to have autonomic impairment ranging from grade I to grade IV. Studies which were done earlier reported dysautonomia in 20- 60 % of patients. Either a single test or a minimum number of tests were considered in defining autonomic neuropathy in all the series. The high incidence of autonomic neuropathy in this study may be attributed to increased number of tests the patients were subjected to, small number of study population and majority of patients studied were under poor degree of metabolic control.

The frequency of male and female distribution of autonomic dysfunction was 55% and 35% respectively. Out of 26 male patients studied 22.84% had autonomic dysfunction and all the female patients studied were found to have autonomic neuropathy. There was a highly significant sex difference in the distribution of classes of dysautonomia ($p<0.001$). This difference is mainly due to excess of female patients 50% in grade IV degree in this study. This may also be due to small number of females 35% when compared to 65% of males included in this study. However, this

finding is in accord with Veglio et al, who documented a significant sex difference in distribution of class in his study group comprising 221 Type2 diabetic patients (108 males and 113 females).

In this study it has been found that no significant correlation was found between severity of autonomic neuropathy and age. Majority of patients (43.76%) with grade IV autonomic neuropathy were found to be in the age group of 40 to 50 years. No significant correlation was found between duration of diabetes and severity of autonomic dysfunction in this study- 95% of patients with grade IV dysautonomia were found in the 6 to 10 years duration, which comprises a total of 8 patients and 4 patients(that is <75%) in the 11 to 15 years duration group. 55% of patients with grade II dysautonomia were in the duration group 1 to 5 years. Only two patients had the disease duration more than 15 years. One with 16 years of diabetes and the other with 20 years of diabetes. The patient with 20 years of disease duration was found to have grade IV autonomic impairment with all the tests abnormal except atropine test. Her fasting and postprandial blood sugar values were 172 mg% and 202 mg% respectively. The other patient with disease duration of 16 years was with grade I dysautonomia was found to have only deep breathing test abnormal. His fasting and postprandial blood sugar values were 104 mg% and 168 mg%. This suggests that the degree of metabolic control is an important factor that decides severity of autonomic impairment rather than the duration of diabetes.

Of the 6 (15%) patients with disease duration less than one year which include 4 newly detected diabetic patients 3 were found to have grade IV autonomic neuropathy, one patient grade III and two grade II dysautonomy. This may be attributed to insidious onset and asymptomatic nature of the disease and to difficulty in determining the exact onset of the disease in Type 2 diabetic patients. It is evident

from this study that there is a gradual increase in the severity of autonomic impairment with worsening degree of metabolic control, with increase in mean fasting and post prandial blood glucose values from 158mg% and 225 mg% for grade 0 (normal) to 210 mg% and 264 mg% respectively for patients with grade IV dysautonomia.

Among all the variables studied the degree of metabolic control was found to have strongest correlation with the extent of diabetic autonomic neuropathy ($p<0.01$). Patients in the poor control group (Mean fasting blood glucose 219 ± SD 42.8 mg% and postprandial blood glucose 272 ± SD 49.2 mg%) tend to have greater incidence of autonomic symptoms. They also showed greater proportion of patients with grade IV diabetic autonomic neuropathy compared with good control (52 % vs 28 % $<p<0.05$). This is in accordance with the results of the Diabetes Control and Complication Trial (DCCT)[58] which emphasise the need to maintain near normal glycemic state in order to prevent the progression of late complications of diabetes mellitus.

Patients with Type 2 Diabetes Mellitus are treated with varying combinations of oral hypoglycemic agents and insulin by different physicians. A variety of reports appear periodically claiming relative advantage of a single regimen over the other in preventing long term complications of diabetes. However, the results of this study did not show any correlation between the type of treatment regimen (whether OHA/ OHA & INSULIN) and the degree of autonomic impairment. This lack of effect was seen to persist even in comparison between patients undergoing regular or irregular treatment. An interesting observation in this study has been that 50 % of patients were on "Regular" treatment had poor metabolic control (Mean fasting and post - prandi al blood sugar values 219 ± SD 42.8 mg % and 272 ± SD 49.2 mg %) respectively.

This also reinforces the fact that the quality of glycemic control is the most important factor rather than the type of treatment or regularity in the prevention or progression of diabetic autonomic neuropathy.

Results of this study showed that 60 % of patients had grade I autonomic neuropathy and 26.7%had grade IV dysautonomia in over weight and obese group <Body mass index 24.9.) In the non obese group 40 % of patients were found to be with grade 1 and 73.3 % with grade IV autonomic impairment.

This suggests that there exists no correlation between body mass index and severity of autonomic neuropathy.($p>0.05$).

It has been found in this study 15 patients had grade IV autonomic impairment out of which 80 % were in the proteinuric group (24 hour urine protein 150 mg) and only 20 % were in the non proteinuric group (24 hour urine protein 150mg). This is statistically signifigant ($p<0.01$) suggesting that there exist a significant correlation between increased protein excretion and severity of autonomic damage. Result of this study showed out of 15 patients with grade IV dysautonomia 40% were in the group of serum cholesterol > 200 mg% and 60 % in the group of serum cholesterol <200 mg%, suggesting that no significant correlation exist between hypercholesterolemia and severity of autonomic neuropathy.

CONCLUSIONS

1. 90% of patients studied had prevalence of diabetic autonomic neuropathy.
2. Parasympathetic involvement was seen in 82.5% of patients while sympathetic involvement was seen in 37.5%
3. Parasympathetic involvement generally occurs earlier than sympathetic involvement.
4. Evidence of prevalence of autonomic dysfunction may be discovered even in asymptomatic patients by applying the tests described in the study.
5. Nocturnal diarrhoea and urinary symptoms had the greatest correlation with the severity of autonomic impairment.
6. Among the tests performed, the heart rate response to deep breathing and to postural change from lying to standing were found to be the most sensitive in detecting prevalence of autonomic neuropathy.
7. The squatting test may be used as an early marker of prevalence of subtle autonomic impairment, even in asymptomatic diabetics.
8. A battery of tests is more accurate in assessing the degree of involvement of the autonomic system rather than a single test.
9. No correlation was found between the severity of dysautonomia and age, sex, body mass index or duration of diabetes.
10. There was an increased incidence of proteinuria in those with advanced autonomic neuropathy.
11. Hypercholesterolemia did not affect the severity of dysautonomia significantly in diabetic patients.
12. The type of treatment given did not correlate significantly with severity of

autonomic damage in this study.

13. Most patients with advanced grades of autonomic impairment also had evidence of peripheral neuropathy in the form of delayed motor nerve conduction velocity as assessed by means of electrophysiological testing.
14. Among all the variables included in this study, the degree of metabolic control was found to have the strongest correlation with prevalence of diabetic autonomic neuropathy.

SUMMARY

This study revealed a high prevalence of autonomic neuropathy in Type2 Diabetes mellitus patients. This was also evident even in asymptomatic patients. The squatting test can be used as an early marker of dysautonomia. The degree of metabolic control was the factor which had the strongest association with severity of autonomic impairment. Thus, this study underscores the value of tight metabolic control in the ideal management of Type2 Diabetes mellitus.

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yes	platform+medline	author	author	
	Hans J. Woerlea, Christoph Neumannb, Silvia Zschaub,			

Stephanie Tennera, Andrea Irsiglerb, Joerg Schirraa, John E. Gerichc, Burkhard Gökea Diabetes research and clinical practice vol77 aug 2007.

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR. IVAN A JONES,** Post graduate in the Department of General Medicine, Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations.

Place :

Date :

Signature of participant

PROFORMA

Name : Age : Sex :

Occupation : IPNO : DOA :

Duration of Diabetes:

Treatment : DIET/OHA/OHA & INSULIN / INSULIN / NONE

REGULAR / IRREGULAR

HEIGHT : Cms WEIGHT : BMI : F/H : YES/NO

SYMPTOMS AND SIGNS

POSTURAL HYPOTESION IMPOTENCE

DYSPHAGIA DISTURABANCE OF SWEATING

VOMITING INCREASED GUSTATORY SWEATING

GASTRIC FULNESS TINGLING AND NUMBNESS

NOCTURNAL DIARRHOEA ASSENT KNEE JERK

CONSTIPATION ASSENT ANKLE JERK

STRAINING AND HESITATION PUPILARY CHANGES

WEAKNESS OF STREAM OTHERS

SENSATION OF INCOMPLETE EMPTYING

DECREASED FREQUENCY OF MICTURATION

OVER FLOW INCONTINENCE

RESTING HEART RATE :

BEAT TO BEAT HEART RATE VARATION :

DEEP INSPIRIATION : (Min R-R Nit) : msec

DEEP EXPIRATION : (Max R-R Int) : msec

HEART RATE RESP ONSE TO STANDING :

LYING (R-R Int) : msec STANDING : 15^{th} BEAT (R-R Int) : msec

30^{th} BEAT (R-R Int) : msec

30^{th} / 15^{th} RATIO :

SQUATTING TEST

PHASE 1 : msec

PHASE 2: msec

PHASE 3 : msec

SqTv RATIO :

SqTs RATIO :

BP RESPONSE ON STANDING

SUPINE BP : mm Hg STANDING BP : mm Hg

SYSTOLIC BP FALL : mm Hg

HAND GRIP TEST

BP BEFORE TEST : mmHg BP DURING TEST : mmHg

DIASTOLIC BP RISE : mm Hg

HR CHANGES TO Inj ATROPINE

BEFORE InJ (R-RInt) : msec RATIO ;

AFTER Inj (R-RInt) : msec

BIO CHEMICAL DATA:

BLOOD SUGAR: FASTING : mg% Hb : gms%

BLOOD SUGAR PP : mg%

BLOOD UREA : mg%

SERUM CREATININE : mg%

SERUM CHOLESTEROL : mg%

24 Hr. URINE PROTEIN :

ULTRA SONOGRAM ABDOMEN :

KEY TO MASTER CHART

ATROPINE TEST:

At__bf−R−R interval in msec before atropine

At_af—R-R interval in msec after atropine

At_ra-Atropine test ratio

Ar - Atropine test result

Sbl, Dbl-Systolic, diastolic BP lying

Sbs, Dbs-Systolic, diastolic BP standing

Sbf-Systolic BP fall

Pr-Postural fall result

HANDGRIP TEST:

HI, H2-Systolic,diastolic BP before handgrip

H3,H4-Systolic,diasto1ic BP after handgrip

Rd-Diastolic BP rise

Hr-Handgrip test result

Pa, Pb, Pn-Parasympathetic tests: abnormal, borderline, normal

Sa, Sb, Sn- Sympathetic tests: abnormal, borderline, normal

GRD-Grading

Cvp, Cvm-Conduction velocity: Pop 1iteal,Median

Rp, Rm-Results: pop 1iteal,median

Fbs, Pbs-Fasting, postprandial blood sugar

Cho-Cholesterol

Urp-24 hours urine protein

Bu-Blood urea

Sc-Serum Creatinine

Hb-Hemoglobin

Usg-Ultrasonogram

0 - Oral hypoglycemic agents

0&I - Oha & Insulin,

SYMPTOMS AND SIGNS:

P - Present: A - Absent

TEST RESULTS:

N - Normal: B - Borderline : A - Abnormal D - Delayed

MASTER CHART

	Name	Age	Sex	Drn	Trt	Reg	Doc	Ht	Wt	Bmi	Ph	Gf	Nd	Cn	Us	Im	Ds	Tn	Kn	An	Ec	Rh	Dbi	Dbe	Ei_ra	Ei_r	Ls_15	Ls_30	Ls_ra	Lr	Vl_du	Vl_af	Vl_ra
1	logambal	65	F	2	0	R	FAIR	150	45	20	-	P	-	-	-	-	-	-	A	A	-	94	640	640	1	A	600	640	1.07	N	520	600	560
2	podhum ponnu	45	F	5	0	R	POO	150	47	21	P	P	P	-	-	-		P	-	-	-	75	720	800	1.11	B	640	720	1.13	N	600	720	520
3	asha	23	F	6	0	R	POO	140	46	23	P	P	-	P	-	-	P	P	-	A	N	88	640	680	1.06	A	600	600	1	A	480	520	600
4	natarajan	52	M	0	N	N	POO	176	70	23	P	P	-	P	-	-		P	-	A	-	88	680	720	1.06	A	600	600	1	A	560	680	520
5	logesh	51	M	2	O	R	FAIR	165	50	23	-	P	-	P	-	P	P	P	-	A	N	107	520	560	1.08	A	520	520	1	A	440	720	560
6	dhanabal	40	F	1	O	I	POO	152	53	23	P	P	-	-	-		P	P	-	-	-	107	560	600	1.07	A	480	480	1	N	480	520	580
7	senthil	28	M	2	O	I	POO	155	47	20	-	P	-	-	P	P	P	-	-	-	-	115	480	520	1.08	A	480	520	1.08	N	520	430	560
8	elangovan	55	M	7	O&I	I	POO	162	39	15	P	P	P	P	P	P	P	P	A	A	-	94	600	640	1.07	A	560	560	1	A	560	560	720
9	karthik	58	M	12	O	R	FAIR	172	64	22	-	-	-	P	-	P		P	-	A	C	68	720	800	1.11	B	640	680	1.06	N	640	680	520
10	pushpa	65	F	8	O	I	POO	148	50	23	P	P	-	-	-	-	P	P	-	-	-	115	480	520	1.08	A	440	440	1	A	400	440	600
11	rajendran	65	M	12	O	I	POO	166	45	16	P	P	-	-	P	-	P	P	-	-	-	100	480	560	1.17	B	520	520	1	A	520	560	760
12	rajesh	70	M	2	O	R	GOO	179	65	20	-	-		-	-	-			-	-	-	71	760	840	1.11	B	720	720	1	A	600	720	680
13	kavitha	48	F	8	O&I	R	POO	148	40	18	P	P	P	-	-	-	P	P	-	-	-	115	440	480	1.09	A	440	440	1	A	400	440	520
14	ramaraj	40	M	0	N	N	POO	172	52	18	-	-	-	-	-	-			-	-	-	68	720	840	1.17	B	760	800	1.05	N	680	760	800
15	Pappathi	29	F	3	O	R	GOO	140	58	26	P	P	-	P	-	-	P	P	-	A	-	88	640	720	1.13	B	600	600	1	A	520	600	750
16	murugan	65	M	6	O	R	POO	140	46	23	P	P	-	P	-	-	P	P	-	A	N	88	640	680	1.06	A	600	600	1	A	480	520	840
17	maruthi	57	M	3	O	R	GOO	172	65	22	-	-	-	-	-	-	-	-	-	-	-	68	680	840	1.24	N	680	800	1.18	N	600	800	440
18	magesh	55	M	2	O	R	POO	152	48	21	-	-	-	-	-	-	-	-	-	-	-	68	800	1040	1.25	N	720	800	1.11	N	600	760	600
19	roja	40	F	20	O	I	POO	147	60	28	P	P		P	P	-	P	P	-	A	-	75	840	880	1.05	A	760	760	1	A	760	800	580
20	sathya	36	M	0	O	R	POO	165	56	20	P	-	-	-	-	P	-	-	-	-	-	62	920	960	1.04	A	800	840	1.05	N	760	840	560
21	ravi	30	M	2	O	R	FAIR	154	52	22		-	-	-	-	-	-	-	-	-	-	100	600	600	1	A	560	600	1.07	N	560	600	580
22	savithri	55	F	7	O	R	POO	147	64	30	P	P	-	P	-	-	P	P	-	-	-	107	520	560	1.08	A	520	520	1	A	480	520	560
23	seetharaman	50	M	6	O	I	POO	156	43	18	P	P	-	-	P	P	P	P	-	-	-	65	680	800	1.18	B	680	920	1.35	N	560	600	720

S	At_bf	At_af	At_ra	Ar	Sbl	Dbl	Sbs	Dbs	Sbf	Pr	H1	H2	H3	H4	Rd	Hr	Pa	Pb	Pn	Sa	Sb	Sn	Grd	Fbs	Pbs	Urp	Bu	Sc	Cho	Hb	Usg
A	520	440	1.18	B	130	90	120	86	10	N	130	90	136	106	16	N	2	1	1	0	0	2	II	198	240	912	30	1	200	8.8	N
A	640	600	1.07	A	140	80	90	60	50	A	100	70	114	76	6	A	4	0	0	2	0	0	IV	310	392	600	38	2	200	9.8	N
A	800	680	1.18	B	120	90	110	80	10	N	120	90	136	106	16	N	3	1	0	0	0	2	III	264	296	196	48	1.5	144	9.4	N
A	600	520	1.15	B	140	90	110	70	30	A	110	80	120	86	6	A	2	2	0	2	0	0	IV	244	308	252	28	1	240	9.6	N
A	840	680	1.24	N	120	80	114	74	6	N	130	70	150	90	20	N	1	2	1	0	0	2	II	122	188	340	28	0.9	168	10.6	N
A	760	640	1.19	B	160	90	150	86	30	A	160	90	170	100	10	A	0	3	1	2	0	0	I	216	280	90	35	1	152	10.8	N
A	760	600	1.27	N	130	100	150	90	30	A	180	100	200	116	16	N	1	1	2	1	0	1	IV	168	232	378	28	0.9	172	10.2	N
A	680	640	1.06	A	150	80	130	70	20	B	160	80	180	94	14	B	4	0	0	0	2	0	III	240	272	247	24	0.9	248	10	N
A	600	480	1.25	N	110	70	100	70	10	N	110	70	124	90	20	N	2	1	1	0	0	2	II	148	272	441	23	0.7	112	10.2	N
A	880	680	1.29	N	120	80	110	70	10	N	100	70	150	90	20	N	0	0	4	0	0	2	0	160	280	134	28	0.8	168	11.2	N
A	560	440	1.27	N	140	80	120	70	20	B	140	80	160	100	20	N	2	0	2	0	1	1	II	248	300	90	30	1	246	9.4	N
A	640	600	1.07	A	120	80	110	70	10	N	130	90	146	104	14	B	2	1	1	0	1	1	II	148	192	340	20	0.8	200	10.4	N
A	480	400	1.2	B	120	809	100	70	20	B	120	90	130	90	0	A	3	1	0	1	1	0	IV	216	288	196	42	1	204	9.8	N
A	460	440	1.05	A	150	90	120	70	30	A	150	90	160	94	4	A	4	0	0	2	0	0	IV	248	288	420	45	0.8	192	9.2	N
A	1040	600	1.67	N	110	80	104	76	6	N	110	80	140	92	12	B	0	1	3	0	1	1	0	240	264	260	30	1	176	10.6	N
N	720	640	1.13	B	124	80	114	80	10	N	120	80	140	96	16	N	1	2	1	0	0	2	II	148	192	198	20	8	200	11.2	N
A	880	680	1.29	N	110	80	90	70	20	B	100	70	130	90	20	N	0	2	2	0	1	1	I	188	280	260	28	0.8	192	10	N
A	880	640	1.38	N	150	80	136	80	14	B	136	80	160	100	20	N	0	0	4	0	1	1	0	104	160	260	33	1	208	11.4	N
A	760	600	1.26	N	110	70	90	60	20	B	110	70	120	86	16	N	2	1	1	0	1	1	I	306	360	225	30	1	214	9.8	N
A	800	680	1.18	B	120	90	120	84	30	A	150	90	160	96	6	A	3	1	0	2	0	0	IV	172	202	214	43	1.2	224	11.6	N
A	760	720	1.08	A	100	70	90	70	10	N	100	70	120	80	10	A	3	1	0	1	0	1	IV	280	360	240	47	2.5	196	11.2	N
N	1000	800	1.25	N	150	90	110	60	40	A	140	70	150	76	6	A	1	1	2	2	0	0	IV	152	180	85	28	0.8	200	9.8	N
A	600	480	1.25	N	120	70	100	60	20	B	120	70	160	100	30	N	2	0	2	0	1	1	II	136	216	225	33	1	176	9.8	N

24	pushparani	60	F	15	O&I	R	GOO	151	65	29	P	P	-	P	P	-	P	P	A	A	N	79	640	680	1.06	A	600	640	1.07	N	600	640	520
25	suganya	47	F	2	O&I	R	POO	152	57	25	P	P	-	-	P	-	P	P	A	A	C	94	560	640	1.14	B	520	560	1.08	N	480	560	840
26	sunder	60	M	3	O	I	POO	173	45	15	P	P	-	-	-	P	P	P	-	A	-	65	840	880	1.05	A	640	640	1	A	640	760	440
27	balu	60	M	0	N	N	POO	180	62	19	P	P	P	-	-	P	P	P	-	-	-	78	640	680	1.06	A	600	640	1.07	N	600	640	600
28	ashok	65	M	5	O	I	POO	147	35	14	-	-	-	-	P	P		P	-	-	-	100	600	600	1	A	560	560	1	A	520	560	580
29	prem	52	M	0	O	I	POO	156	51	18	P	P	-	-	-	P	P	P	-	-	-	88	680	720	1.06	A	600	600	1	A	640	720	560
30	valli	61	F	3	O&I	R	FAIR	151	56	25	-	-	-	-	-	-			-	-	-	107	440	480	1.09	A	480	480	1	A	400	520	720
31	Pappathi	54	F	1	O	I	POO	148	40	18	P	-	-	P	-	-	P	P	-	-	-	107	480	520	1.08	A	480	480	1	A	440	480	520
32	malar	40	F	0	N	N	FAIR	148	70	31	P	P	-	P	-	-	P	P	-	-	-	94	600	680	1.13	B	600	600	1	A	520	680	460
33	vinoth	72	M	2	O	I	FAIR	159	56	22	P	P	-	P	P	P	P	P	A	-	-	88	640	720	1.13	B	640	640	1	A	600	720	680
34	venkatesh	58	M	15	O	I	POO	172	40	14	P	P	-	-	-	-	P	P	-	A	-	94	600	640	1.07	A	520	520	1	A	520	560	760
35	arunachalam	55	M	8	O	I	POO	173	60	20	P	P	-	P	-	P	P	P	-	A	C	100	600	600	1	A	520	520	1	A	520	600	520
36	Xavier	53	M	1	O	R	FAIR	171	65	22	-	-	-	-	-	-	-	-	-	A	-	100	520	560	1.08	A	520	520	1	A	480	560	800
37	vivek	35	M	4	O	I	POO	121	65	21	P	P	-	-	P	P	P	P	-	A	C	94	600	640	1.07	A	640	680	1.06	N	600	640	920
38	manikantan	45	M	8	O	I	POO	173	60	20	P	P	-	P		P	P	P	-	A	C	100	600	600	1	A	600	600	1	A	520	680	600
39	pandyan	55	M	3	O	I	POO	173	45	15	P	P	-	-	-	P	P	P	-	A	-	65	840	880	1.05	A	640	640	1	A	600	720	800
40	krishnan	48	M	15	O	I	POO	172	40	14	P	P	-	-	-	-	P	P	-	A	-	94	600	640	1.07	A	520	520	1	A	520	560	560
41	*saleem	53	M	0	-	-	-	173	45	15	P	P	-	-	-	P	P	P	-	A	-	65	440	480	1.09	A	480	480	1	A	400	520	600
42	*rengaraj	42	M	0	-	-	-	180	62	19	P	P	P	-	-	P	P	P	-		-	78	480	520	1.08	A	480	480	1	A	440	480	520
43	*vijaya	45	F	0	-	-	-	159	65	24	-	-	-	-	-	-	-	-	-	-	-	88	560	680	1.22	N	640	680	1.06	N	520	640	560
44	*malathi	53	F	0	-	-	-	160	48	21	-	-	-	-	-	-	-	-	-	-	-	78	600	760	1.26	N	640	720	1.12	N	520	680	580
45	*vanaja	47	F	0	-	-	-	155	58	24	-	-	-	-	-	-	-	-	-	-	-	88	600	680	1.13	B	640	680	1.06	N	600	720	560
46	* Mariyammal	42	F	0	-	-	-	154	56	24	-	-	-	-	-	-	-	-	-	-	-	88	560	680	1.21	N	680	720	1.06	N	520	680	720
47	*thangaraj	60	M	0	-	-	-	178	65	21	-	-	-	-	-	-	-	-	-	-	-	94	480	520	1.08	A	480	480	1	A	440	480	520
48	*gunasekar	62	M	0	-	-	-	177	63	20	-	-	-	-	-	-	-	-	-	-	-	83	600	680	1.13	B	600	600	1	A	520	680	600
49	*gopal	45	M	0	-	-	-	180	62	21	-	-	-	-	-	-	-	-	-	-	-	88	640	720	1.13	B	640	640	1	A	600	720	920
50	* Sadasivan	75	M	0	-	-	-	179	59	24	-	-	-	-	-	-	-	-	-	-	-	82	600	640	1.07	A	520	520	1	A	520	560	600

A	520	440	1.08	B	110	70	80	60	30	A	110	70	120	80	10	A	3	1	0	2	0	0	IV	224	280	273	45	2	287	9.2	N
A	680	560	1.21	N	130	90	110	80	20	B	130	80	150	100	20	N	1	2	1	0	1	1	II	134	200	216	25	0.8	160	11.2	N
A	600	520	1.15	B	110	70	90	60	20	B	110	70	120	80	10	A	3	1	0	1	1	0	IV	210	240	275	24	0.7	147	9.6	N
N	640	480	1.33	N	150	80	150	70	30	A	180	80	190	96	16	N	1	2	1	1	0	1	IV	124	172	186	32	1	198	9.8	N
A	600	560	1.25	N	110	70	100	60	10	N	110	70	140	86	16	N	2	1	1	0	0	2	II	136	272	162	24	0.8	184	11	N
A	560	480	1.17	B	110	80	110	70	20	B	130	80	150	96	16	N	3	1	0	0	1	1	III	114	196	634	33	1.1	196	11.2	N
A	720	520	1.38	N	116	76	110	74	6	N	110	74	140	90	16	N	0	1	3	0	0	2	0	128	196	242	25	0.8	176	10.8	N
A	640	560	1.14	B	110	70	80	60	30	A	110	70	140	90	20	N	2	1	1	1	0	1	IV	232	260	130	40	1	196	12	N
A	600	480	1.25	N	100	70	90	60	10	N	100	70	110	80	10	A	3	0	1	1	0	1	IV	216	272	260	24	0.8	138	11.2	N
A	640	480	1.33	N	120	80	110	70	10	N	120	80	140	100	20	N	1	1	2	0	0	2	I	144	202	143	33	1	200	11.2	N
A	680	400	1.21	N	130	80	120	70	10	N	130	80	140	100	20	N	1	1	2	0	0	2	I	104	168	1869	55	0.8	214	8.6	N
A	480	400	1.2	B	120	70	110	70	10	N	120	70	140	90	20	N	2	1	1	0	0	2	II	146	216	840	27	1	152	9.6	N
A	600	480	1.25	N	120	80	110	70	10	N	120	80	160	100	20	N	2	1	1	0	0	2	II	176	236	252	37	1	196	9.8	N
A	680	560	1.21	N	140	90	114	80	16	B	140	90	154	100	10	A	2	0	2	1	1	0	IV	128	216	1625	33	1.2	266	8.6	N
A	560	440	1.27	N	120	80	100	70	20	B	120	80	140	96	16	N	3	0	1	0	1	1	III	200	280	625	42	1	198	10	N
A	600	480	1.25	N	140	90	120	80	20	B	140	90	150	108	18	N	0	2	2	0	1	1	I	180	216	189	35	0.8	217	9.8	N
A	640	560	1.14	B	140	90	120	80	20	B	140	90	160	106	16	N	2	1	1	0	1	1	II	188	216	580	28	1.7	238	10	N
N	760	520	1.46	N	110	70	100	70	10	N	110	70	156	94	24	N	0	0	0	0	0	0	-	80	96	84	30	0.8	172	10.8	N
N	920	680	1.35	N	120	80	114	76	6	N	120	80	156	100	20	N	0	0	0	0	0	0	-	78	84	92	35	0.8	200	11.4	N
N	720	560	1.28	N	120	80	106	74	14	N	120	80	158	100	20	N	0	0	0	0	0	0	-	90	110	84	30	0.8	198	10.2	N
N	680	560	1.21	N	110	80	100	76	10	N	114	80	146	98	18	N	0	0	0	0	0	0	-	90	100	96	28	0.8	202	9.8	N
N	680	520	1.41	N	110	80	100	74	10	N	110	80	154	104	24	N	0	0	0	0	0	0	-	60	82	89	22	0.8	186	10.8	N
N	760	520	1.42	N	120	80	110	76	10	N	120	80	150	106	26	N	0	0	0	0	0	0	-	86	100	94	24	0.8	196	11.2	N
N	880	520	1.69	N	120	84	114	80	6	N	120	80	148	102	22	N	0	0	0	0	0	0	-	86	102	90	32	0.9	200	11.2	N
N	640	480	1.33	N	120	70	110	70	10	N	120	70	148	90	20	N	0	0	0	0	0	0	-	88	120	89	24	0.8	175	10.2	N
N	880	440	2	N	114	70	100	70	4	N	114	70	158	96	26	N	0	0	0	0	0	0	-	80	88	92	28	0.8	174	9.2	N
N	680	520	1.42	N	120	70	120	70	10	N	120	70	160	94	24	N	0	0	0	0	0	0	-	88	102	92	30	0.9	194	9.8	N